ARCHIVES OF DISEASE IN CHILDHOOD

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EDITOR OF THE *British Medical Journal*.

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CHRONIC MILIARY TUBERCULOSIS IN CHILDREN*

BY

R. H. FISH, M.D.Camb., M.R.C.P.Lond., D.C.H.,
Senior Assistant Medical Officer, Colindale Hospital, Hendon;
late Senior Assistant Medical Officer, High Wood Hospital for Children, Brentwood.

Survey of literature

The existence of a chronic form of miliary tuberculosis which is not invariably fatal has recently begun to attract the attention of British clinicians. The subject formed the basis of a leading article in the ' British Medical Journal ' in November, 1934[1], and a paper on it was read by Sayé of Barcelona at the last provincial meeting of the Tuberculosis Association at Cambridge[2]. Nevertheless the condition is still looked upon by many as a medical curiosity and only five cases reported by writers from this country have been found. The earliest of these was described by Preston and Jeaffreson[3] in 1925; later three were mentioned by Burton Wood[4, 5], and in 1935 one was reported by Deaner[6] entitled ' Chronic Disseminated Tuberculosis with Erythema Nodosum.' A case showing multiple calcified nodules in both lungs was reported by O'Reilly[7] who regarded it as intermediate in form between the primary focus and miliary tuberculosis.

A study of the foreign literature gives a different impression of the matter. As early as 1845 Waller[8] in Germany made the statement that miliary tuberculosis was not always fatal, and in 1861 in the same country Wunderlich[9] maintained that he often saw evidences of healed miliary tuberculosis while making autopsies. The first detailed report of cases of chronic miliary tuberculosis was by Burkart[10] in 1873: he described four in which the character of miliary tubercles observed in the lungs post-mortem suggested that they had existed for a considerable period before death. In America an early writer on the subject is Longcope[11] who in 1906 described eight cases in which he considered life was prolonged sufficiently for them to be classed as chronic. In 1914 Northrup[12], in the same country, described seven cases. In 1924 Blaine[13] reported three that he had discovered in the stage of calcification. In the French literature the classical work on the subject is that of Burnand and Sayé[14] in 1924, entitled ' Granulies Froides et Granulies Chroniques.' These writers described nine cases. All their patients were in fair general health and afebrile when first examined: two of them died from meningitis, and the diagnosis based on the radiological findings was confirmed at autopsy; of the remainder, all except one had improved, and one had cleared up completely.

With the wider use of radiology that has developed during the last decade, many more publications on the subject under discussion have

* Based upon a thesis submitted for the degree of M.D. Cambridge.

appeared in France, Germany, America, and a few other countries. From America an excellent account is given by Fishberg[15], who states that ' such cases are seen by everyone who meets with many chest cases.' From Germany a good review is provided by Hein[16]; he describes twenty cases, and gives a long list of references. From France, in June, 1934, twenty-four cases were reported in a critical discussion on the subject that took place in Paris[17]. Among these was a patient described by Ferru and Perochon who recovered and remained well for seven years although tubercle bacilli were demonstrated in the sputum. Finally, there is the paper by Sayé[2], referred to previously, in which the writer described a large number of cases classified into different types and even went so far as to say that he had detected miliary tuberculosis by routine x-ray examination in a number of healthy students.

A good account of the condition as it occurs in children is given by Armand-Delille and Lestocquoy[18] in their recently published manual on juvenile pulmonary tuberculosis: the former writer, from his wide experience of tuberculosis in children, has reported many cases of chronic miliary tuberculosis in a number of different publications. Another interesting paper is by Rist et al[19], who describe seven cases of miliary tuberculosis of the lungs of which three were relatively acute while the remaining four recovered; they demonstrate the gradual transition between the acute and chronic forms of the disease. Jochims[20] describes four cases occurring in children: he considers the occurrence of extra-pulmonary manifestations, such as tuberculous arthritis and terminal meningitis, as evidence of the haematogenous origin of the pulmonary nodules. Duken[21] describes eight cases, also in children, in which haematogenous tuberculous lesions of the skin were a prominent feature. Miller[22] describes several others in a long thesis in which he expounds on the subject of haematogenous pulmonary tuberculosis in general. Sachs[23] describes two cases supported by the presence of tubercle bacilli in the sputum that cleared up completely. Valette and Rosenkranz[24] have reported three cases, Edel[25] three, and Marlow[26] two, also associated with cutaneous lesions.

In the majority of cases mentioned so far it was only possible to demonstrate a pulmonary form of chronic miliary tuberculosis. There is evidence, however, that even generalized miliary tuberculosis may pursue a prolonged course and sometimes end in recovery. Among the cases described by Duken[21] is one showing multiple calcified deposits on radiographical examination in both liver and spleen. Similar cases are described by Miller[22] and Hellgren[27]. Opie and Anderson[28] took x-ray photographs of the organs removed from a large number of post-mortem subjects: they report a case in which not only were the lungs, liver, and spleen thickly studded with calcified nodules, but a number of these were also observed on the pia mater over the frontal lobes of the brain. It might be contended that the findings of multiple calcified deposits is insufficient evidence on which to make a diagnosis of healed miliary tuberculosis. Assmann[29], however, describes a patient in whom, in addition to the miliary picture in in the chest skiagram, miliary tubercles were observed on the retina; yet the patient became apparently quite well, and remained so for six months before developing urogenital tuberculosis, of which she finally died. The most striking case of all is the following, reported by Cohn[30] as far back as 1921. In a girl, aged fourteen, the spleen was removed on grounds of a diagnosis of Banti's disease. The organ was found to be studded with typical macroscopic and microscopic miliary tubercles, and similar tubercles were observed on the peritoneal surface of the liver. Following the operation an x-ray photograph was taken of the chest, and this revealed the typical picture of miliary tuberculosis. The girl lived and was observed

over several years. At the end of this period she was quite well; and, except for a slight increase in the physiological pulmonary striation, the radiological appearance of her chest was normal.

Other writers who have reported cases of either chronic or calcified miliary tuberculosis are Baer[31], Kahn[32], Kern[33], Lorey[34], Middleton[35], Pierson[36], Stivelman[37], and Wallgren[38].

Differential diagnosis

In face of the formidable amount of literature on the subject referred to in the foregoing survey, there can be little doubt not only that miliary tuberculosis sometimes runs a chronic course, but also that complete recovery from the disease occasionally takes place. Nevertheless, in view of the scarcity of reports of cases of this type emanating from British writers, a record of further examples occurring in this country should be of interest. Before describing a new series of cases, however, it is necessary to point out that the diagnosis of miliary tuberculosis is not infrequently made on insufficient evidence. A discussion of the possible sources of error in this connexion will therefore not be out of place.

With a skiagram of the chest suggestive of miliary tuberculosis, i.e., showing reasonably small opacities densely distributed over both lung fields, before this diagnosis can be accepted, it must be shown, first, that the opacities seen in the picture represent tuberculous nodules, and second, that these nodules resulted from a dissemination of organisms by the blood stream. In regard to the first of these points a considerable number of non-tuberculous conditions may be mentioned which are liable to simulate the x-ray picture of miliary tuberculosis: among these are pneumoconiosis, carcinomatosis, broncho-pneumonia or bronchiolitis, chronic vascular congestion due to cardiac insufficiency, and disseminated blood following haemoptysis. In regard to the second point, that is the mode of implantation of the nodules, there are two other possibilities besides that of a haematogenous spread. The lesions may be the result of a dissemination of disease via the air passages; the radiographical appearance of a tuberculous broncho-pneumonia is often similar to that of miliary tuberculosis. The other possibility is a disseminated lymphatic pulmonary tuberculosis. The pathology of this is a little difficult to understand as it would appear to entail a spread of disease in a direction contrary to that of the normal lymph flow; nevertheless Pleininger[39] has described a case under the title of 'lymphangitis reticularis tuberculosa,' and Duken[21] also refers to this condition when discussing chronic miliary tuberculosis.

Finally, in relation to the question of the mode of origin of the nodules in chronic miliary tuberculosis, reference must be made to certain hypotheses which, although they do not necessarily indicate a revison of the diagnosis, might nevertheless provide an explanation for the benign course of the illness in these cases and serve to distinguish them pathologically from the

more common acute type of the disease. Burton Wood[4] has drawn attention to the frequent occurrence in these cases of exudative or allergic manifestations such as epituberculosis and the benign juvenile type of pleural effusion; he suggests that chronic miliary tuberculosis may itself be a similar exudative type of phenomenon. He points out that the skin reaction to tuberculin is usually strongly positive in chronic miliary tuberculosis, whereas an acute miliary tuberculosis it is not infrequently negative. He also remarks that the opacities seen in the skiagrams in chronic miliary tuberculosis tend to be of a coarse type with a somewhat blurred outline, and that their resolution often occurs with surprising rapidity. In relation to Burton Wood's observations, experiments that were carried out by Nicaud[17] are of considerable interest. By the intravenous injection of dead tubercle bacilli he was able to produce, in the lungs of rabbits, lesions similar to those he had found at autopsy in a case of chronic miliary tuberculosis in which the patient had died following an operation for pyloric stenosis. Nicaud interpreted this experiment as an indication that tuberculous toxins alone could give rise to x-ray appearances simulating miliary tuberculosis. Taking cognisance of Burton Wood's observations, it might be suggested as an alternative possibility that the stippling of the skiagrams in the recoverable variety of the illness is a manifestation of an exudative or allergic reaction produced by dead tubercle bacilli disseminated throughout the lungs. All these theories require further investigation.

Report of cases at High Wood Hospital

After this discussion of the possibilities that may lead to an erroneous diagnosis of chronic miliary tuberculosis, it is proposed to report a number of cases which are considered to be genuine examples of this condition observed among children admitted to High Wood Hospital during the last four years. Like the acute variety of the disease, chronic miliary tuberculosis appears to occur particularly frequently in young subjects. High Wood Hospital is a favourable institution for cases of this type because it receives all children affected with pulmonary tuberculosis requiring institutional treatment under the London County Council tuberculosis scheme. First will be described six fatal cases, and then four in which recovery has taken place.

Case 1. SUBACUTE MILIARY TUBERCULOSIS OF LUNGS.

A boy, aged ten years, was admitted with a history of influenzal pneumonia nine months previously, with cough and gradual emaciation since. A right pleural effusion had occurred three months previously and a skiagram one month previously showed 'mottling of both lungs.' On admission he showed a fair general condition, was rather pale and thin, with slight cough, and a subnormal temperature. There were harsh breath sounds all over the chest with a few fine crepitations at both apices. There were some enlarged cervical glands. His other systems were normal. Sputum was unobtainable and gastric lavage was not carried out. The

Mantoux reaction was negative to 1 in 10,000, but positive to 1 in 1,000. A skiagram of the chest showed dense stippling of both lung fields, and slight pleural thickening on right side (fig. 1).

The boy was kept lying flat in bed on an open air balcony. His condition gradually deteriorated. Pyrexia developed three months after admission, and he died in a cachetic condition, five-and-a-half months after the pulmonary stippling was first detected radiographically.

Autopsy (at another hospital) revealed both lungs densely studded with miliary tubercles; further details were not obtainable.

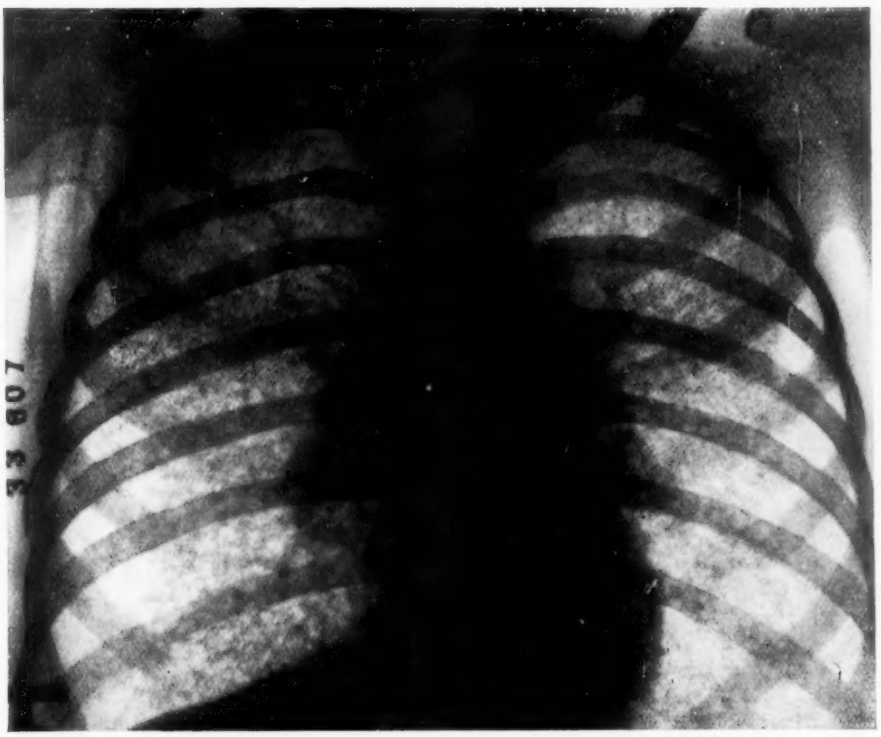
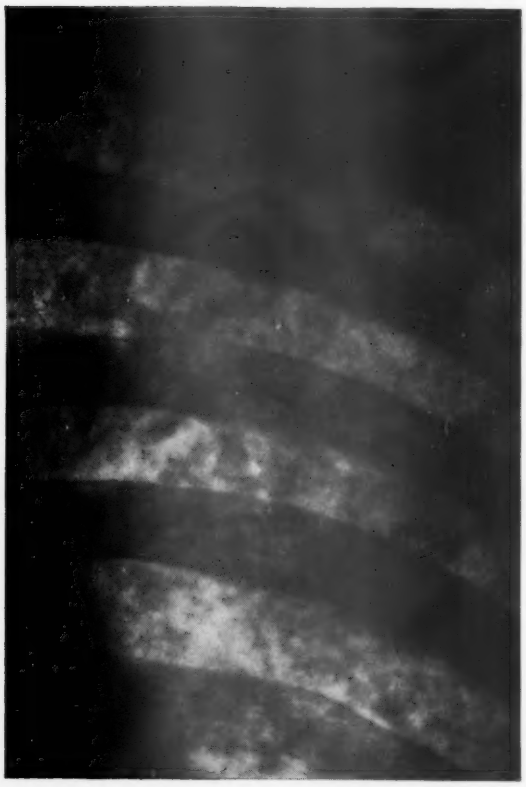


FIG. 1.

Case 2. CHRONIC MILIARY TUBERCULOSIS OF LUNGS WITH DEATH FROM TUBERCULOUS ENTERITIS.

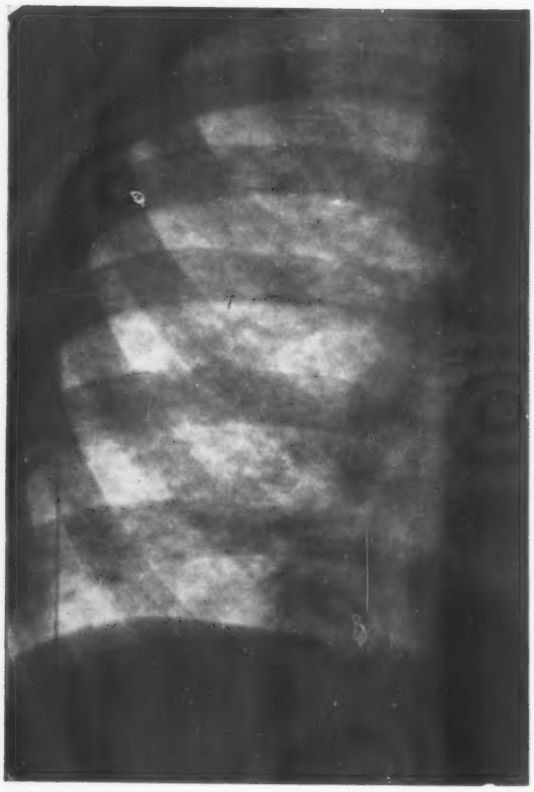
A boy, aged thirteen years, had never recovered since an illness diagnosed as left basal pneumonia three months before admission. On admission his general condition was very poor; there was emaciation, a malar flush and cyanosis, but no cough. His temperature was subnormal. Examination of the chest showed a slightly impaired percussion note and diminished air entry at left base. The breath sounds were a little harsh, with crepitations at both apices. There were some enlarged glands on both sides of neck. The other systems were normal. Sputum was unobtainable but gastric lavage revealed tubercle bacilli on direct examination of centrifugalized material, a finding which was confirmed by inoculation of a guinea pig. The Mantoux reaction (1 in 10,000) was positive. A skiagram of the



Case 2.

Case 4.

Case 5.



Case 6.

FIG. 2.—Shows detail of pulmonary stippling in cases 2, 4, 5 and 6. In case 6 note also bulging upper mediastinum and shadow extending downwards from right hilum.

FIG. 3.—Healing miliary tubercles.

FIG. 4.—As fig. 3 under $\frac{1}{6}$ objective.

chest showed a fine fluffy stippling of both lung fields with some larger shadows at the apices (fig. 2), and some haziness in the left costo-phrenic angle suggesting a resolving pleural effusion.

The boy was kept lying flat in bed and given a course of intramuscular injections of solganal B. oleosum. His condition remained about stationary at first, but later began to deteriorate. A sudden turn for the worse with pyrexia of 99–100° F. set in about six months after admission. Diarrhoea appeared with tumidity of the abdomen. Death however did not take place till seven months after admission.

Autopsy revealed both lungs studded with miliary tubercles and a few larger caseous nodules, mainly in upper lobes. There were also numerous caseous cervical and mediastinal glands, and tuberculous ulceration of small intestine. Other organs were unaffected.

Microscopical sections of lung tissue showed numerous miliary tubercles containing tubercle bacilli and giant cells. Many of these tubercles showed evidence of healing; they were ringed round by and infiltrated with fibrous tissue staining pink in van Giesen preparations (fig. 3 and 4).

Case 3. CHRONIC MILIARY TUBERCULOSIS OF LUNGS WITH DEATH FROM MENINGITIS.

A girl, aged one-and-a-half years, was admitted to a general hospital for double otorrhoea and debility. A skiagram of chest showed mottling of both lung fields, a wide upper mediastinum. and an epituberculous type of shadow extending out from the right hilum (fig. 5). She was transferred to

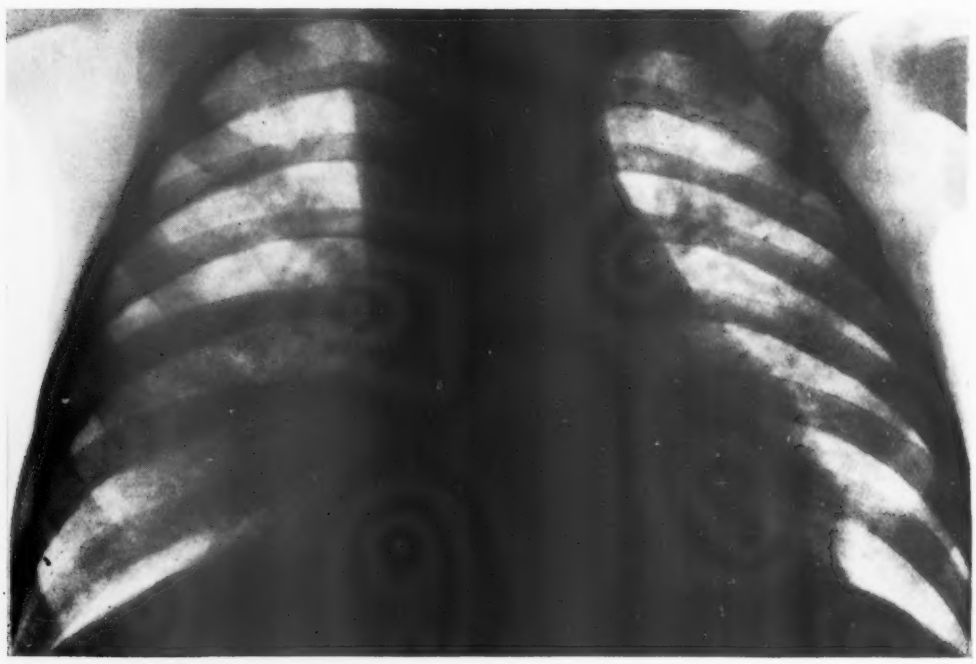


FIG. 5.

High Wood two months later and on admission there she was an emaciated, ill-looking child with slight cyanosis and a troublesome cough. The temperature range was 97°–99° F. Examination of the chest showed normal percussion and prolonged expiration all over with scattered crepitations on

both sides, especially at right base. The abdomen was distended and resistant to palpation. The urine was normal. There was profuse bilateral aural discharge which was not examined for tubercle bacilli. Numerous large matted glands bulged out on both sides of the neck. No other clinical abnormalities were found. The sputum was unobtainable and gastric lavage was not carried out. The Mantoux reaction (1 in 10,000) was positive. A skiagram of chest showed little change from previous one, except that the shadow extending out from right hilum was smaller.

The child was kept in bed as still as possible with aid of restrainers. Cardboard splints were applied to her neck. Her condition improved considerably at first, although intermittent pyrexia persisted. Her weight increased until, six months after admission, she had gained five-and-a-half pounds. At this stage the pyrexia began to increase again and the child became drowsy. She finally died in state of coma ten months after the first skiagram was taken.

Autopsy revealed tuberculous meningitis, numerous large caseous cervical and mediastinal glands, and in the left kidney a large tuberculous pyonephrosis. Small punctate miliary tubercles were scattered through both lungs.

Microscopical sections of lung tissue showed two distinct types of miliary tubercles. The first, containing tubercle bacilli and giant cells, were presumably of recent origin; the second, showing as nodules of pink-staining, fibrous tissue in van Giesen preparations, were presumably of long standing. It seems probable that these latter had been responsible for the original pulmonary stippling, and that a fresh haematogenous dissemination of organisms had occurred recently giving rise to fresh miliary deposits in the lungs and also to meningitis.

Case 4. CHRONIC MILIARY TUBERCULOSIS OF LUNGS WITH TEMPORARY IMPROVEMENT FOLLOWED BY FATAL MENINGITIS.

A girl, aged nine years, with history of recent pain in right chest, of uncertain duration, with slight cough, anorexia, and loss of weight was admitted in a poor general condition, pale and emaciated. She had a slight cough and complained of pain in the right side of chest. The temperature range was 97·5–99·5° F. The percussion note over the chest was impaired and the breath sounds were faint at right base; there were harsh breath sounds and a few crepitations at right apex. No other clinical abnormalities were found. A specimen of sputum was obtained and found to contain tubercle bacilli. The Mantoux reaction (1 in 10,000) was strongly positive. A skiagram of the chest showed a moderate-sized pleural effusion on the right side, slight upper mediastinal widening, and a fine generalized stippling of both lung fields.

The child was kept at rest in bed for five months, during which time her condition improved steadily. At the end of this period she had gained 7 lb. in weight and had been completely free from pyrexia for a month. A fresh skiagram showed the pulmonary stippling still present (fig. 2), although the effusion had absorbed. The child was allowed to get up for periods increasing up to four hours a day. At this point pyrexia reappeared and she was returned to bed. Signs of meningitis soon appeared, and death followed, nine months after pulmonary stippling was first demonstrated in a skiagram.

Autopsy revealed tuberculous meningitis, caseous hilar and mediastinal glands, and numerous small miliary tubercles throughout both lungs.

Case 5. CHRONIC MILIARY TUBERCULOSIS OF LUNGS SHOWING TEMPORARY IMPROVEMENT.

A girl, aged twelve years, with a history of left pleural effusion ten weeks previously was admitted in a fair general condition, pale but moderately well nourished. There was no cough or sputum. The temperature range was 97–98·6°. There was an impaired percussion note and weak air entry at both bases, particularly at the left and a few fine crepitations at both apices. No other clinical abnormalities were present. The Mantoux reaction (1 in 10,000) was positive. A chest skiagram showed a wide upper mediastinum, pleural thickening on both sides, and a fine stippling all over both lung fields (fig. 2).

The child was kept in bed for four months, during most of which time she was apyrexial, and then allowed to get up for gradually increasing periods. By six months after admission she had gained 10 lb. in weight, but a fresh skiagram taken at this time still showed the pulmonary stippling little changed. She had reached the stage of six hours up in the day, when the pyrexia reappeared; from this time on, despite return to bed, her condition steadily deteriorated. A cough developed, and tubercle bacilli were demonstrated in the sputum. The pyrexia increased and the child died in a cachectic state eleven months after the disease had been first detected by x-ray. Autopsy was not carried out, as the child was transferred to another hospital a few days before death.

Case 6. CHRONIC MILIARY TUBERCULOSIS OF LUNGS WITH TEMPORARY IMPROVEMENT FOLLOWED BY FATAL MENINGITIS.

A girl, aged one year, with a history of cough following measles two months previously, had spent two months in a general hospital where skiagrams showed ' mottling throughout both lungs.' On admission she was in poor general condition, underweight for her age, but not markedly emaciated. Cough was present, and wheezy respiration. The temperature range was 97·5–101·1° F. There were slight impairment of percussion note and some coarse crepitations at the right base, the breath sounds being a little harsh all over. There were some large glands on both sides of neck. No other clinical abnormalities were noted. Sputum was unobtainable. Tubercle bacilli were demonstrated by inoculation of gastric lavage material into a guinea pig. The organisms were shown to be of human type by culture on Jensen's modification of Loewenstein's medium. The Mantoux reaction (1 in 10,000) was positive. A skiagram of the chest showed a fine, fluffy stippling of both lung fields, upper mediastinal widening, and a shadow of irregular outline extending downwards from the right hilum (fig. 2).

The child was kept in bed as still as possible with the aid of restrainers. Her condition gradually improved for seven months, at the end of which time her temperature had been normal for six weeks and she had gained 8 lb. in weight. At this point she developed an attack of tonsillitis, and from this time on her condition began to deteriorate. Pyrexia recurred a month later, and increased gradually until meningitis set in leading to the death of the child twelve months after pulmonary stippling was first demonstrated by x-ray.

Autopsy revealed tuberculous meningitis, caseous cervical glands, and large caseous glands in upper mediastinum. Both lungs were densely studded with miliary tubercles.

Microscopical sections of lung tissue showed both recent and healed miliary tubercles as in case 3, but intermediate stages in the healing process

were also demonstrable. Fig. 6 shows on the right a healed nodule of fibrous tissue, and on the left a recent miliary tubercle containing a giant cell. Fig. 7 shows the healed nodule under the $\frac{1}{6}$ objective.

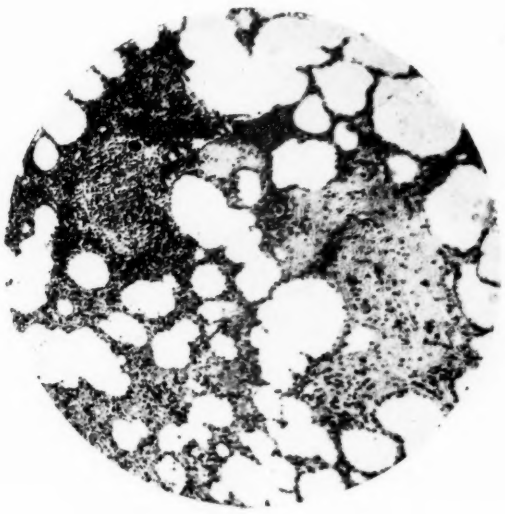


FIG. 6.

FIG. 7.

Case 7. MILIARY TUBERCULOSIS OF LUNGS WITH OSSEOUS LESIONS. MARKED IMPROVEMENT AFTER SIXTEEN MONTHS' ILLNESS.

A boy, aged three years, with a history of contact with a phthisical mother, had had before admission six months' intermittent pyrexia following

whooping cough. On admission he was in a poor general condition, pale and emaciated. There was no cough. The temperature range was 97–100° F. There were harsh breath sounds all over the chest, and a few post-tussive crepitations at both bases. There were numerous enlarged cervical glands. No other clinical abnormalities were noted. The sputum was unobtainable. Tubercle baccili were demonstrated by inoculation of gastric lavage material into a guinea pig. The Mantoux reaction was negative to 1 in 10,000 but positive to 1 in 1,000. A skiagram of the chest showed a wide upper mediastinum and a somewhat coarse type of mottling over both lung fields (fig. 8).

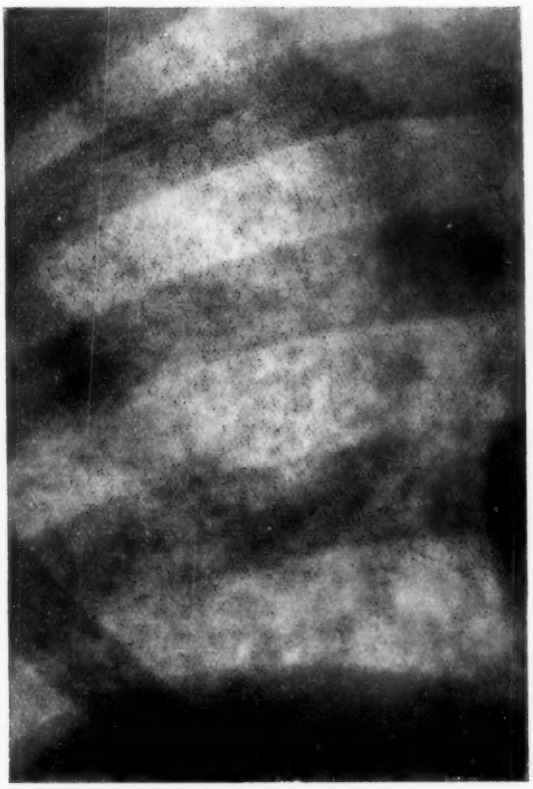
The boy was kept in bed, as still as possible with restrainers, and given a course of injections of solganal B. oleosum. His condition gradually deteriorated during the next nine months, during which time the pyrexia persisted and he lost 4 lb. in weight. Three months after admission he developed tuberculous disease in the right elbow. Nine months after admission tuberculosis of the cervical spine manifested itself by a retropharyngeal abscess. The boy was then transferred to Queen Mary's Hospital, Carshalton, where he was treated on a spinal frame. In a skiagram taken at this time the pulmonary stippling remained little changed. Rupture of the retropharyngeal abscess occurred with discharge of tuberculous pus. Later, tubercle bacilli were also demonstrated in pus from an abscess over the right elbow. Since being placed on the frame the boy's condition improved steadily, and seven months after this (sixteen months after pulmonary mottling was first detected by x-rays) he was stated to be in fair general condition and to have had a subnormal temperature for five months.

Case 8. MILIARY TUBERCULOSIS OF LUNGS WITH RECOVERY.

A boy, aged ten years, with a history of increasing lethargy following pneumonia nine months previously, and the report that a skiagram had shown miliary tuberculosis two-and-a-half months before was admitted acutely ill. He showed a marked malar flush, emaciation, dyspnoea, and a slight cough. The temperature range was 99–101·2° F. The only abnormal physical signs in the chest were a few fine crepitations in left anterior axillary line. Other systems were normal. Sputum was unobtainable. Gastric lavage revealed tubercle bacilli after inoculation of a guinea pig. The Mantoux reaction (1 in 10,000) was positive. A skiagram of the chest showed typical dense miliary stippling of whole of both lungs, a fluffy wedge-shaped shadow extending outwards from the right hilum, and a wide upper mediastinum (fig. 8 and 9).

The boy was put on absolute rest in bed, and the temperature subsided in a week's time. He was kept in bed and given a course of injections of solganal B. oleosum. Six weeks after admission there was a sudden recurrence of pyrexia (101° F.) which coincided with the appearance of three typical papulo-vesicular tuberculides on the dorsum of the left hand. After this his condition improved steadily. Pulmonary stippling was still present in a skiagram taken five months after admission, but six months after this both lung fields appeared clear (fig. 10). Only then was the boy allowed to get up. He gained weight steadily, and at the present time, eighteen months after pulmonary stippling was first demonstrated, he is up all day and appears extremely fit.

Case 7.



Case 8.

Case 9.

Case 10.

FIG. 8.—Shows detail of pulmonary stippling in cases 7 to 10.

FIG. 9.—Case 8 on admission.

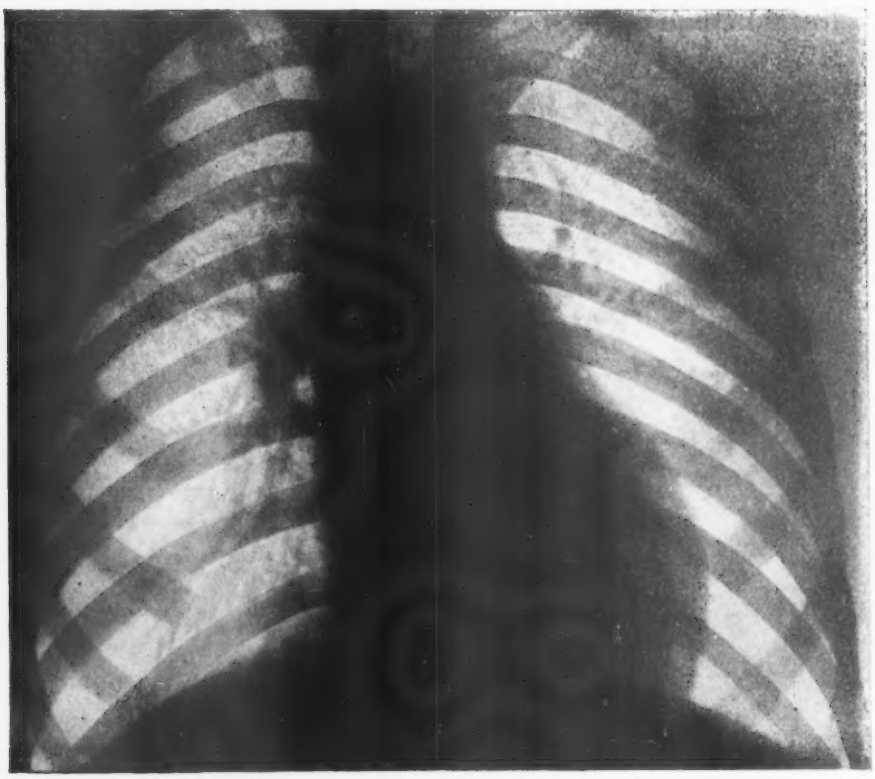


FIG. 10.—Case 8 eleven months later.

Case 9. MILIARY TUBERCULOSIS WITH RECOVERY. LUNGS AND POSSIBLY LIVER AND SPLEEN AFFECTED.

A boy, aged three years, was admitted to a general hospital with ascites five months before transfer to High Wood. Tubercle bacilli were found in the sputum at this time, and miliary tuberculosis was diagnosed from x-ray pictures. On admission to High Wood he was in fair general condition, rather fat, but flabby and a little flushed. There was no cough or sputum. The temperature range was 97–99° F. There was an impaired percussion note at the base of the right lung with harsh breath sounds all over the chest and crepitations at right base. Examination of the abdomen showed no free

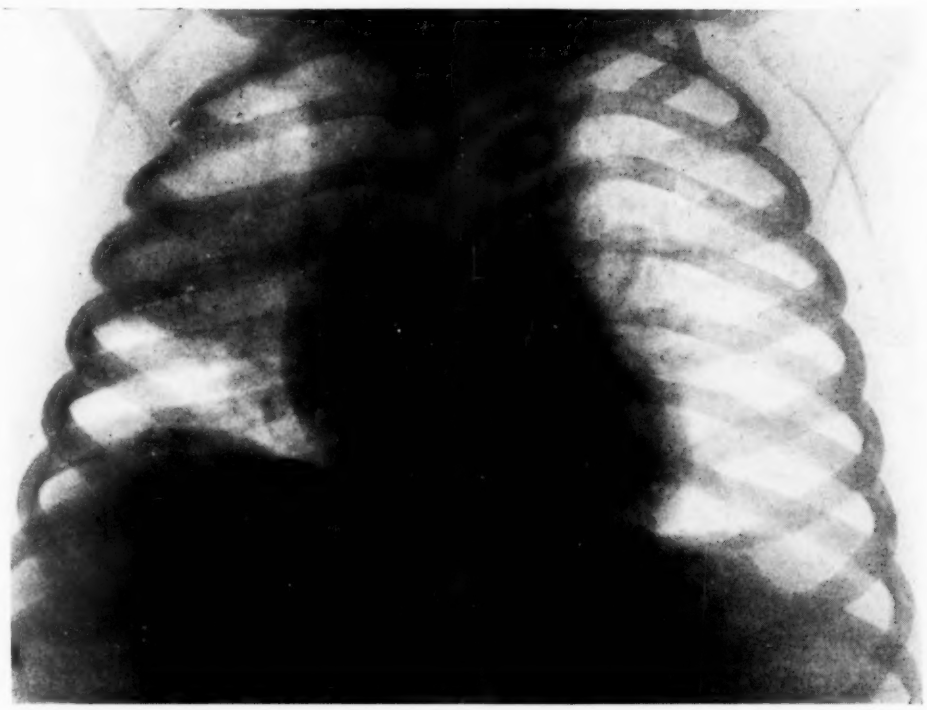


FIG. 11.

fluid. The liver edge was palpable one inch below the costal margin and the tip of the spleen was palpable. A fluctuant swelling over the left mastoid process was incised, and yielded pus containing tubercle bacilli. The Mantoux reaction (1 in 10,000) was positive. A skiagram of chest showed marked widening of upper mediastinum, a shadow in the right mid zone of the epituberculosis type (possibly due to collapse of the middle lobe), and a faint but definite stippling of both lung fields (fig. 8 and 11).

The boy was kept in bed as still as possible, and a course of injections of solganal B. oleosum was given. Pyrexia persisted for six months, but ultimately subsided. By ten months after admission the liver and spleen were no longer palpable, and the sinus over the mastoid process had healed. Since this time his condition has continued to improve, and at the present time, twenty-one months since the disease was first demonstrated by x-rays, he is getting up all day and very fit. A recent skiagram shows no evidence of pulmonary stippling.

Case 10. CHRONIC MILIARY TUBERCULOSIS OF LUNGS, WITH ABDOMINAL, CUTANEOUS, OSSEOUS, AND CEREBRAL TUBERCULOUS LESIONS, TERMINATING IN RECOVERY.

A boy, aged six years, with a history of persistant pyrexia following measles five months before was admitted with fair general condition and nutrition. He had a slight cough. The temperature range was 97–99·5° F. There was an impaired percussion note at the left base with crepitations at both bases, more on the left. The abdomen was prominent and ' doughy.' There was discharge from the right ear. No other clinical abnormalities were noted. The Mantoux reaction (1 in 10,000) was positive. A skiagram of the chest showed a wide upper mediastinum, a shadow of epituberculous type in the left lower zone, and a rather coarse fluffy type of mottling of both lung fields (fig. 8 and 12).

The boy was kept in bed as still as possible. Pyrexia persisted continuously for one year and intermittently for most of a second year. Tubercle bacilli were demonstrated in the sputum on two occasions. In serial skiagrams the pulmonary stippling gradually became less definite, but it was still detectable two years after admission. At this time the boy had gained 7 lb. in weight since admission and had reached the stage of being up all day and afebrile. After a few weeks, however, the pyrexia recurred, and a number of small crusty papules appeared on both buttocks. A large abscess full of tuberculous pus next appeared on the left buttock, and a skiagram showed rarification of the greater trochanter of the left femur. The papules healed leaving pitted scars, and the disease of the femur was successfully treated by open operation at Queen Mary's Hospital, Carshalton.

The boy was allowed up again, and was then found to be blind in the right eye; examination of the fundus showed complete optic atrophy. Further examination revealed exaggerated deep reflexes and an extensor plantar response on the right side. Lumbar puncture and x-ray examination of the skull revealed no abnormalities; nevertheless a diagnosis of healed cerebral tuberculomata seems the most likely one. The other possibility is a healed meningitis. At the present time, three-and-a-half years after admission, the boy has been up all day for nine months and is very fit. A skiagram taken three years after admission showed both lung fields quite clear except for a calcified patch at the left base and a few tiny calcified spots in the right lung (fig. 13).

Discussion

There can be little doubt that all the fatal cases described above, i.e., cases 1 to 6, represent genuine examples of miliary tuberculosis of a chronic type. The post-mortem findings were conclusive in five out of the six, and in the remaining one, case 5, the characteristic x-ray picture combined with the presence of tubercle bacilli in the sputum and the fatal termination of the illness should satisfy most critics. Nevertheless the duration of the illness in these cases varied from five-and-a-half to eleven months taken from the time the disease was first demonstrated by x-rays, and in all but the first two members of the group indubitable clinical improvement took place although this was only of a temporary nature. The most important feature of these cases is the demonstration of both healed and healing miliary tubercles in microscopic section of the lungs. All intermediate stages could be observed between typical acute miliary tubercles and nodules of pure fibrous tissue. These nodules were situated in the interstitial tissue disconnected from the bronchial tree; they were also isolated from each other

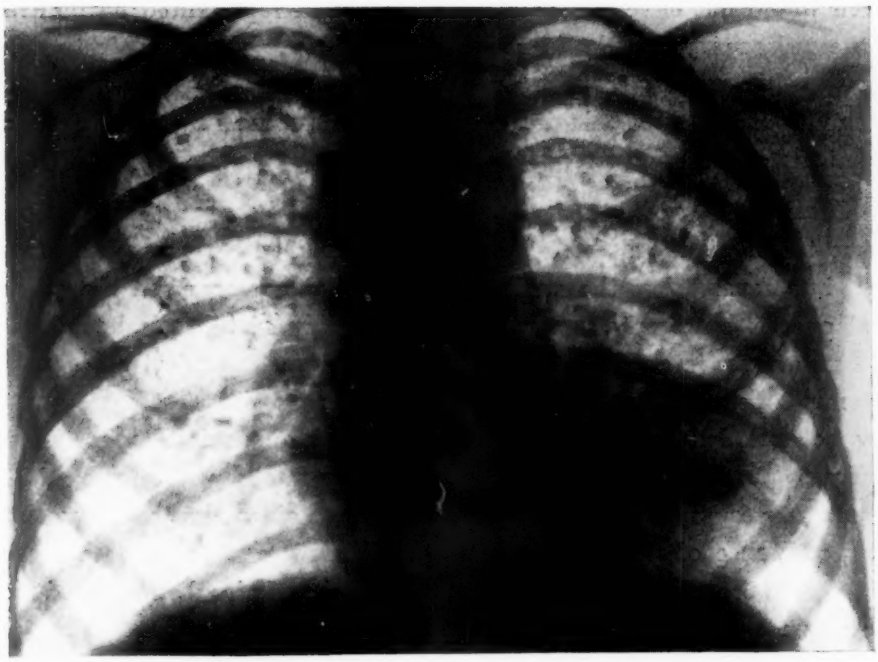


FIG. 12.—Case 10 on admission.

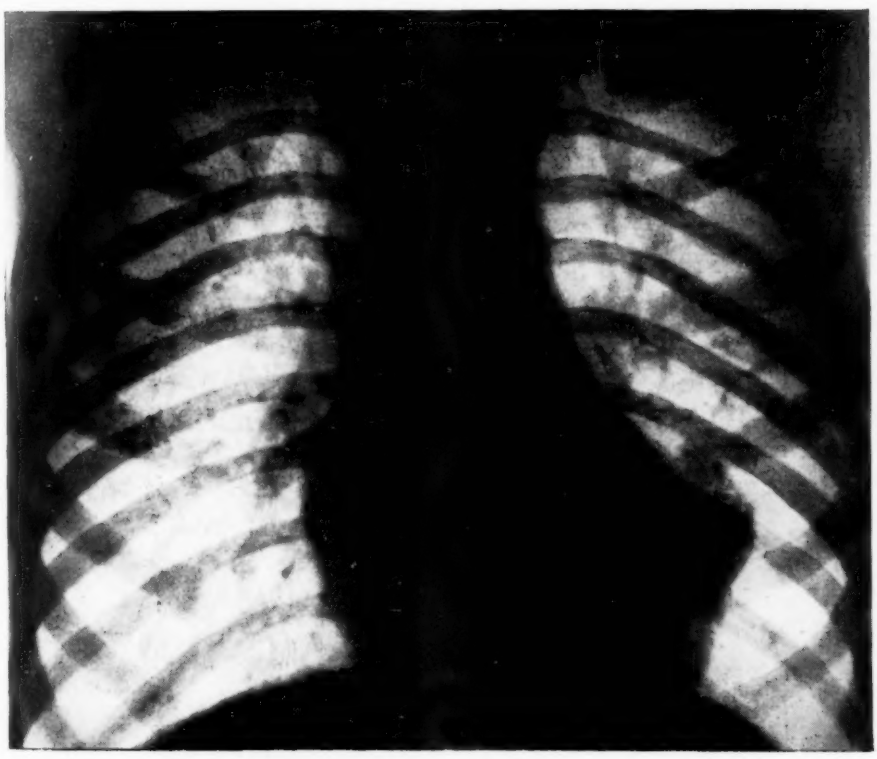


FIG. 13.—Case 10 three years later.

which would not have been the case if they had represented an infiltration of the pulmonary lymphatic network. Further it was possible to demonstrate multiple tubercle bacilli in many of them: this finding excludes the possibility that the pathological changes were produced by toxins from dead organisms as was suggested by Nicaud.

Cases 7, 8, 9 and 10 are of particular interest because of the favourable course taken by the illness. Post-mortem findings are necessarily lacking here, but nevertheless the similarity between these cases and the other six fatal ones is extremely suggestive. The finding of tubercle bacilli in the sputum or gastric contents in these cases is evidence against a diagnosis of any non-tuberculous condition. Among other possibilities, carcinomatosis may be excluded as being practically unheard of in childhood; the same applies to pneumoconiosis particularly as there was in no instance a history of exposure to any special dust that might have given rise to this condition. The persistence of the stippling over periods of many months excludes a non-specific broncho-pneumonia or bronchiolitis and also disseminated blood. The absence of cardiac lesions excludes vascular congestion.

A feature of particular significance in regard to the pathology of cases 7 to 10 is the occurrence in all four of them, at some period during the course of the illness, of definitely established extra-pulmonary tuberculous lesions which could only have arisen following a discharge of tubercle bacilli into the blood stream. The presence of these lesions constitutes a strong piece of evidence in favour of the haematogenous origin of the original deposits. In case 7 the right elbow and cervical spine were affected; in case 8 cutaneous tuberculides occurred; in case 9 there was a tuberculous abscess over the left mastoid process, and the hepatic and splenic enlargement pointed towards a haematogenous abdominal tuberculosis. The most striking example, however, is case 10: here, in the first instance, the skiagram of the lungs indicating miliary lesions was associated with tuberculous peritonitis and with a chronic otitis media which may well also have been of tuberculous origin. Two years later a fresh generalization of infection occurred, resulting in tuberculous disease of the femur, cutaneous tubercles, and probably tuberculomata of the brain. It is of interest to note that extrapulmonary tuberculous lesions were also a feature of three of the similar but fatal cases described previously. In case 3 there was a tuberculous kidney, and also, as in case 10, otitis media of undetermined etiology; tuberculous meningitis occurred in three instances, cases 3, 4 and 6. It is noteworthy that in both groups of cases, in every instance in which the development of an extra-pulmonary lesion was observed, the appearance of the latter was heralded by an increase or recrudescence of pyrexia such as might be expected to accompany a discharge of organisms into the blood,

It is evident that all these cases, whether fatal or otherwise, were of a type showing a tendency to recurrent episodes of tuberculous bacillaemia. It is surely more than probable on this ground alone that the initial deposition of organisms in the lungs in all of them followed a similar episode of this nature.

In both fatal and non-fatal cases an interesting feature of the skiagrams was the marked widening of the upper mediastinal shadow. In cases 3, 4 and 6, at autopsy, this x-ray appearance was shown to be due to the presence of numerous large caseous paratracheal glands. It is now generally accepted that the spread of tuberculous disease in a child, following primary infection of the lung, takes place first along the pulmonary lymphatics to the hilar glands. From the hilar glands the disease may spread further to the tracheo-bronchial glands, and thence to the paratracheal glands in the upper mediastinum. This group forms the subject's last line of defence in the struggle to obstruct the organisms in their passage towards the blood-stream: the final stage of the journey, in cases where this last barrier has been passed, may reasonably be supposed to occur with little difficulty through either the thoracic duct or the main right lymph duct. A tendency to tuberculous bacillaemia is thus to be expected in association with caseation of the upper mediastinal glands; the presence of the latter feature in a large proportion of the cases in the series is a further point in favour of a haematogenous origin for the pulmonary lesions. It is noteworthy that cases 1 and 2, in which upper mediastinal widening was not evident in the skiagrams, are the only ones in which there was no evidence whatever of a recurrence of bacillaemia after the initial pulmonary dissemination of the virus.

It still remains to consider Nicaud's suggestion that a dissemination of dead tubercle bacilli might be responsible for the lesions in certain non-fatal instances of miliary tuberculosis; there are, however, strong arguments against the applicability of this hypothesis to any of the cases in the present series. The finding of numerous tubercle bacilli in a single nodule in the microscopic sections from three fatal cases has already been referred to. In the other cases, if the causative organisms had been dead at the time of their implantation in the lungs, it would seem impossible that they should have been found apparently intact in the sputum or gastric contents many months later. What is more, in four instances the organisms obtained by gastric lavage proved virulent to guinea pigs. With regard to Burton Wood's conception of a benign exudative variety of miliary tuberculosis, there are certain features of the cases which would at first sight appear to favour this. Epituberculous manifestations occurred in five

members of the series and pleural effusion in four, also the Mantoux test was positive in all cases; further a coarse variety of pulmonary stippling with a blurred outline to the individual opacity was observable in many of the skiagrams. But these last features were by no means constant findings throughout the series: in cases 3 and 4 for example, the skiagrams showed an abnormally fine variety of stippling, and in case 8 the opacities appeared small and well defined although they ultimately cleared up completely. A significant point against Burton Wood's view as applied to these cases is the long period over which the stippling persisted in the skiagrams in most instances. In case 10 the opacities could still be detected in the films two years after they were first demonstrated; it is unlikely that this would have been the case if the lesions had been of a purely exudative nature. Thus, taking everything into consideration, the hypotheses of Nicaud and Burton Wood both appear insufficient to explain the pathology of the examples of chronic miliary tuberculosis reported in this series. There seems no reason to suppose that in the initial stage of the illness the nodules present in the lungs of these cases differed in any essential feature from the tubercles of the acute miliary disease.

A final point worth mentioning is the gradual transition in type that appears from case to case throughout the series. The absence of any sharp line of demarcation between the acute and chronic forms of miliary tuberculosis has already been demonstrated by Rist et al[17], whose work was referred to in the survey of the literature given above. The present set of cases, arranged for this purpose in order of severity, help to bear out this point. In case 1 the illness pursued an inexorable course towards a fatal termination without any signs of a remission occurring. Since the lesions were confined to the lungs and the picture was not complicated by meningitis, the six months duration of the illness here is not much longer than might be expected in accordance with the prevalent conception of miliary tuberculosis as an inevitably fatal disease. The cases in the series gradually become more chronic until case 10 in which the child has been under observation for over three years. It would appear that all intermediate degrees of severity of the condition may be met with between classical acute miliary tuberculosis and a chronic form which may last several years and ultimately clear up altogether. This observation is a strong argument in support of the pathological unity between all these cases.

An abortive form of miliary tuberculosis

Cases 1 to 10 were selected for publication as being particularly striking examples of chronic miliary tuberculosis. Actually among children at High Wood Hospital the writer has observed a considerable number of other

similar cases which, although not quite so convincing, nevertheless showed clinical and radiological features strongly suggestive of the same condition in a milder form. In some of these the disease was of a localized type limited for example to one lung or only part of one lung; in others the stippling seen in the skiagrams covered both lung fields, but was of a fine punctate variety that tended to clear up relatively rapidly. The latter x-ray appearance was frequently seen in conjunction with a shadow of the epituberculosis type extending out from the hilar region; it was also almost invariably associated with x-ray evidence of tuberculous glands in the upper mediastinum. The course of the illness was usually favourable in this type of case; nevertheless in two instances recorded meningitis developed shortly after the child was allowed exercise. It seems probable that these cases were examples of an abortive form of miliary tuberculosis in which the growth of the nodules was checked at an early stage: possibly the organisms deposited in the lungs were of an abnormally low virulence. Although it must be admitted that gross examples of chronic tuberculosis are of comparatively rare occurrence, these abortive forms appear to be considerably more common. With the spread of the practice of examining juvenile contacts by x-ray, they are likely to be detected increasingly frequently. Their early recognition and treatment should assist materially in reducing the incidence of tuberculous meningitis which is still an important cause of death in childhood.

Treatment

A study of cases 1 to 10 makes it clear, not only that no sharp line of demarcation exists between the acute and chronic forms of miliary tuberculosis, but also that it is frequently impossible to determine the prognosis of any given case at the outset. Patients appearing desperately ill may sometimes recover, while others in relatively good general condition are liable to go steadily downhill. It follows therefore that treatment should be considered in every case. One point stands out above all others; that is the paramount importance of rest. Any child whose chest skiagram suggests miliary tuberculosis should be kept in bed until the stippling has completely disappeared from the picture. Any earlier termination than this involves risk of disaster. Certainly it is not enough to wait only until the pulse and temperature become normal; tragic evidence of the truth of this is provided by cases 4 and 5, and the two other instances mentioned in the last section, in which a fatal relapse followed shortly after exercise was allowed. Absolute rest, as opposed to simple confinement to bed, is a matter very difficult of attainment in a young patient; nevertheless an attempt should be made to keep the child lying flat at least until the acute

stage of the illness has passed. The remarkable improvement that took place in case 7 after the boy was placed in a spinal frame suggests that in certain instances this method of treatment might just turn the balance, even in the absence of spinal disease.

All the children in this series were treated on open air balconies. In view of the good results obtained, it seems likely that this factor was beneficial. The only other form of treatment used in these cases was gold therapy. Good results have been claimed from this method by Sayé[10]; and three out of the four cases on which it was used at High Wood Hospital did well. Solganal, which can be given intramuscularly, is probably the best form to give the metal in these toxic cases owing to the slow absorption by this route. In a child aged three the initial dose given was 0·005 gm.; this was increased up to a final dose of 0·2 gm. after fifteen weekly injections.

Summary and conclusions

After a survey of the literature and a discussion of the differential diagnosis, a series of ten cases of chronic miliary tuberculosis occurring in childhood is described. Recovery took place in four of these cases; microscopic sections of the lungs in three of the fatal examples demonstrated the healing process in individual miliary nodules. The cases are discussed and the following conclusions are reached.

(1) Miliary tuberculosis runs a chronic course more frequently than is generally recognized; recovery occurs in a fair proportion of these chronic cases.

(2) Recovery is commonest when the nodules are confined to the lungs, but it may also take place in generalized cases and even when the onset of the illness is moderately acute.

(3) The pathology of the lesions in chronic and acute cases is essentially the same.

(4) Healing of individual miliary tubercles takes place by a process of fibrosis which usually leads to their complete disappearance from the pulmonary skiagrams.

(5) Massive caseous glands in the upper mediastinum are a frequent finding in the juvenile type of chronic miliary tuberculosis; the presence of these glands may be responsible for the tendency to recurrent episodes of tuberculous bacillaemia which is a feature of these cases.

(6) Any one of these episodes may give rise to fatal meningitis; the risk of this complication occurring is, however, considerably diminished if strict rest in bed is maintained until the x-ray picture is clear.

Acknowledgments

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MILK CURD—ITS MECHANISM AND MODIFICATION*

BY

I. NEWTON KUGELMASS, M.D.

(From the New York City Children's Hospital.)

The mechanism of milk clotting has been discussed in a previous report[1]. Each of the clotting constituents of milk affect not only the course of coagulation but the character of the clot. At first a colloidal, non-settling precipitate forms which agglomerates to a dense mass, the curd. The set gel contracts and squeezes out the whey, a phenomenon called syneresis. The character of the clot has been studied to determine the modes of modifying milk in order to obtain a clot favourable for infants' digestion.

Curd-toughness of milk was determined by Hill's method[2] as shown in figure 1. It affords a quantitative measure of the tensile strength of milk curd upon peptic digestion. A series of 100 c.c. samples of milk were brought to 37° C. in special glass jars, the curd knife placed in position, 10 c.c. of coagulant added and after ten minutes a spring balance hooked through a loop in the knife. It was then drawn through the curd by even tension, the amount required being read directly on the balance. The lower the resistance the greater the accuracy of reproduction. The appearance of the cut curds of various milks are shown in figure 2.

Cow's milk varies greatly in curd tension. It is an individual characteristic of the cow rather than the breed, and cows from the same breed give milks with curds ranging from very soft to very hard. What determines the character of the clot? Several workers[3] have studied a variety of factors which take part in the production of curd tension of milk, but consideration of the previous paper[1] indicates that the only factors determining the toughness of the curd are the clotting constituents of milk —casein, calcium ions, rennet. All others modify the clot superficially.

(A) Effect of milk clotting constituents on curd tension

The concentration of the clotting constituents were correlated with the curd tension of milk. Casein was determined by the method of Waterman, calcium by the method of Clark, and rennet added in increasing amounts.

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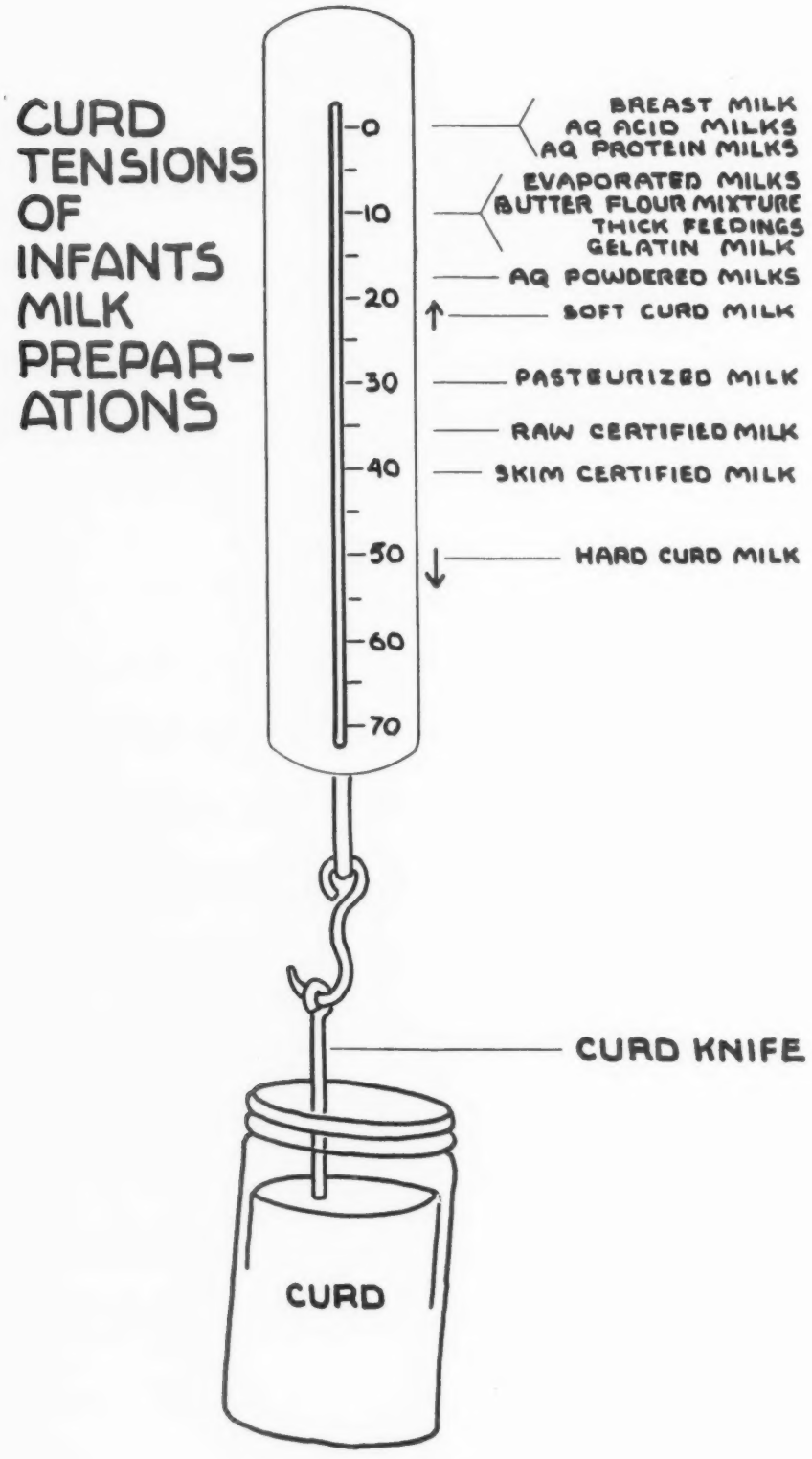
CURD TENSIONS OF INFANTS MILK PREPAR-ATIONS
0
10
20
30
40
50
60
70
BREAST MILK
AQ ACID MILKS
AQ PROTEIN MILKS
EVAPORATED MILKS
BUTTER FLOUR MIXTURE
THICK FEEDINGS
GELATIN MILK
AQ POWDERED MILKS
SOFT CURD MILK
PASTEURIZED MILK
RAW CERTIFIED MILK
SKIM CERTIFIED MILK
HARD CURD MILK
CURD KNIFE
CURD

FIG. 1.

FIG. 2.—Character of curd.

TABLE 1.

EFFECT OF MILK CLOTTING CONSTITUENTS ON CURD TENSION AND CLOTTING TIME.

CASEIN PER CENT.	CURD TENSION GM.	CLOTTING TIME MINUTES	CALCIUM PER CENT.	CURD TENSION GM.	CLOTTING TIME MINUTES	RENNET C.C.	CURD TENSION GM.	CLOTTING TIME MINUTES
1·0	15	40	0·10	5	40	2	6	50
1·5	20	32	0·11	10	25	3	7	40
2·0	27	15		15	15	4	9	25
2·5	45	10	0·13	30	11	5	15	18
3·0	95	7	0·14	55	9	6	19	15
3·5	130	4	0·15	70	7	7	22	13
4·0	160	2	0·16	85	6	8	26	12
			0·17	100	5	9	35	9
						10	39	8
						14	40	7
						12	50	6

There is practically a direct relationship between each of these clotting constituents and curd tension; the higher their concentration the greater the toughness of the curd. But the casein effect is most determining upon the tensile strength of the milk curd. The auto-catalytic curve is almost upright (fig. 3). At low casein concentrations there appear a linear relationship between the casein content and the curd tension of milk. The minimum transition point at which milk develops hard curd is about the 2·5 per cent. level of casein. Slight rises in the casein content markedly increase the curd tension. Indeed, between the 2·5 per cent. casein and the 3·5 per cent. casein represents a difference in curd tension from about 30 gm. to about 150 gm. in this series. Above 3·5 per cent. casein content the rate of increase in curd tension abates asymptotically. The physico-chemical significance of this S-shaped curve will be considered below in discussing the volume changes during clot formation with varying concentration of casein in milk. Apparently soft curd milk is delimited by an upper casein concentration of 2·5 per cent. The calcium and rennet relationships are linear, the former affecting the curd tension more than the latter. A calcium content of about 0·125 per cent. delimits soft curd milk, for above this value the greater the increase in the calcium content the greater the curd tension. And conversely, the higher the clotting time the lower the curd tension. Rennet has the least effect upon the tensile strength of the curd for relatively large amounts of rennet raise the curd tension but slightly in comparison with the other clotting constituents. But there is a gradual and steady rise in the curd tension with increasing concentrations of rennet. Curd tension thus varies inversely with the clotting time.

(B) Effect of milk dilution with water on curd tension

Hard curd milks obtained from Sheffield Farms were diluted with increasing amounts of water and the curd tension of each clotted mixture

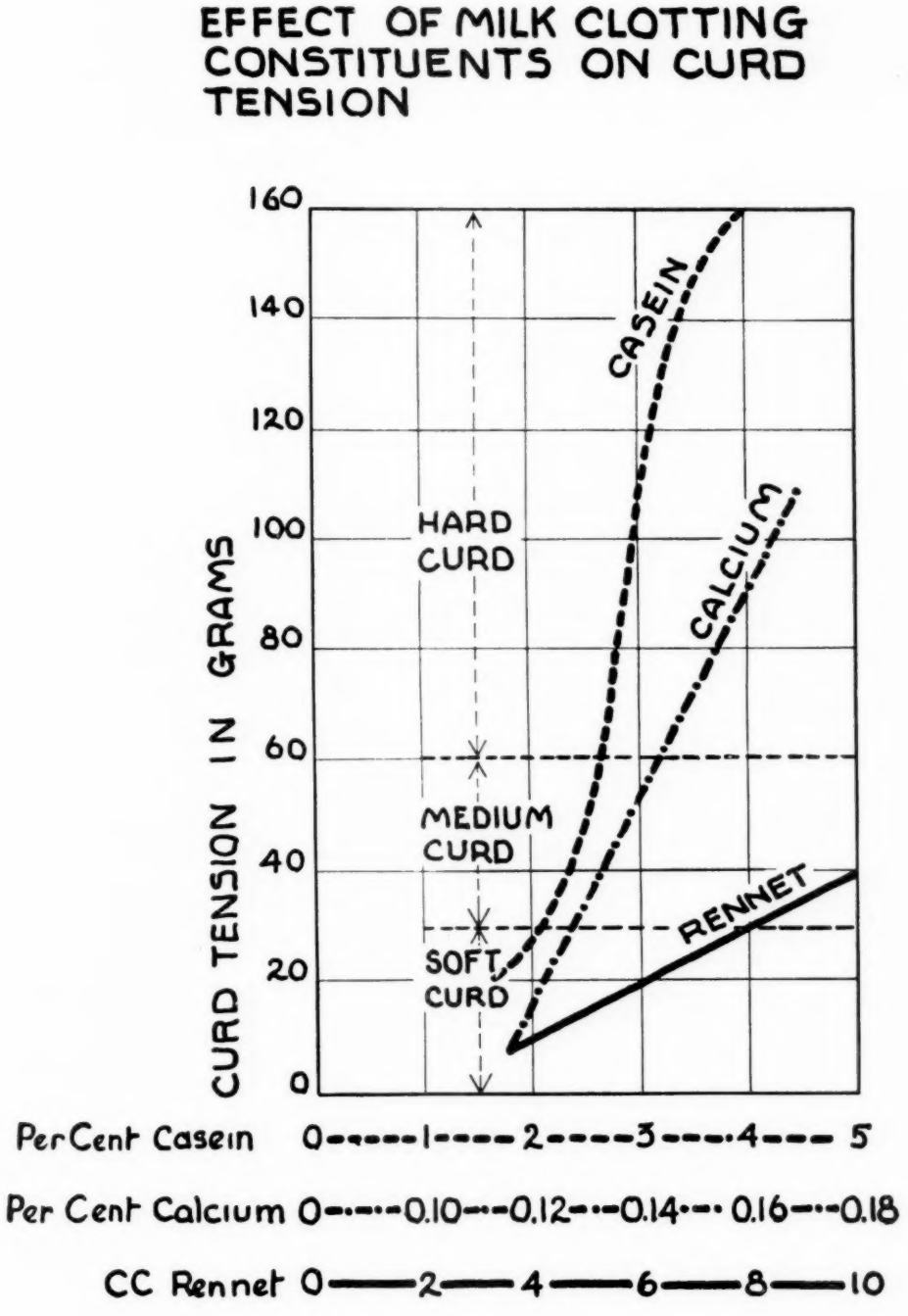
EFFECT OF MILK CLOTTING CONSTITUENTS ON CURD TENSION
CURD TENSION IN GRAMS
160
140
120
100
80
60
40
20
0
HARD CURD
MEDIUM CURD
SOFT CURD
CASEIN
CALCIUM
RENNET
Per Cent Casein 0----1----2----3----4---5
Per Cent Calcium 0----0.10---0.12---0.14---0.16---0.18
CC Rennet 0——2——4——6——8——10

FIG. 3.

determined. The relationship between dilution and curd tension is parabolic (fig. 4). The curd tension diminishes rapidly with dilution. The slope of the curve indicating a transition point which marks the beginning of soft curd milk at 50 per cent. dilution of raw milk. In other words if dilution

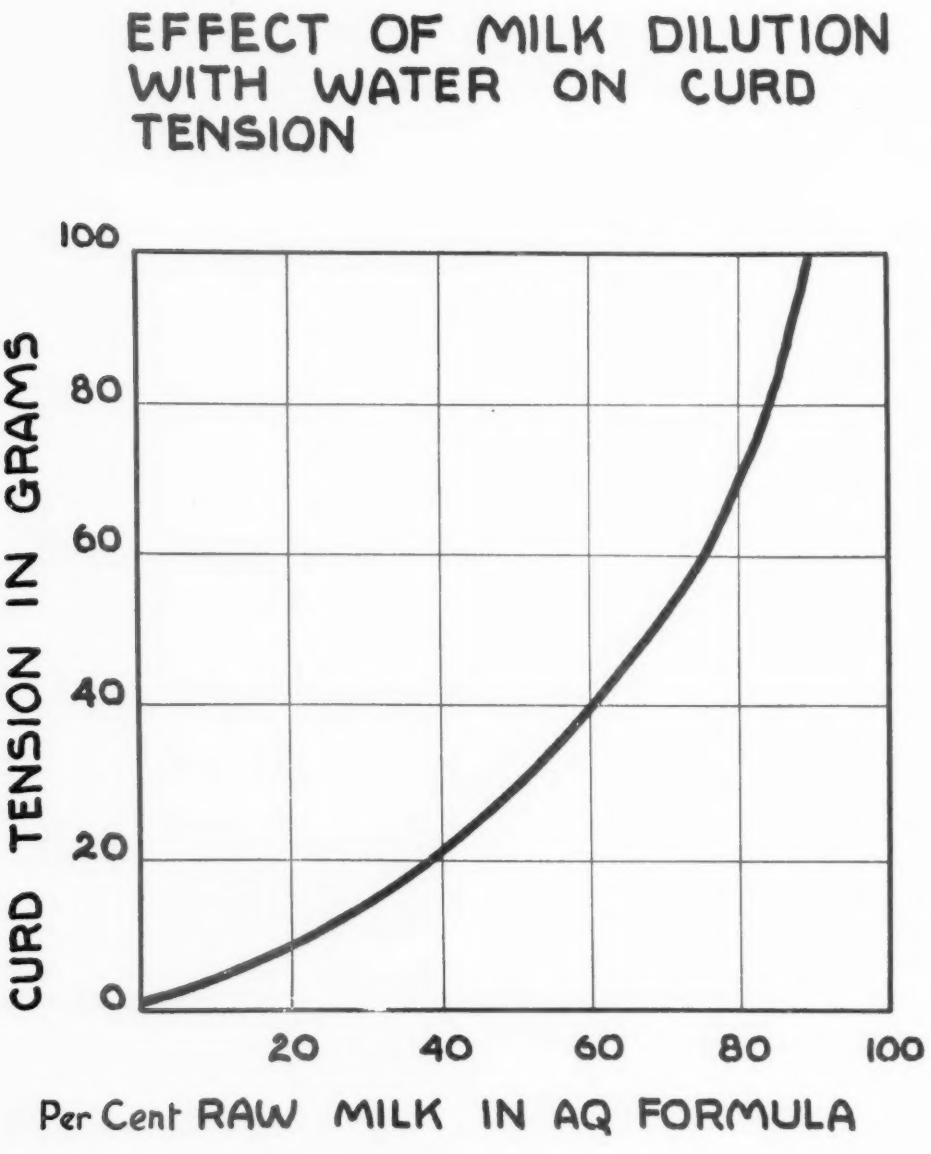

FIG. 4.

alone were the only modification of raw milk in infant feeding the one to one ratio of milk to water would suffice to soften the curd without any other procedure. The fact that half-diluted milk initiates soft curd formation also follows from a consideration of the previous experiment. It has been seen that hard curd milk is relatively high in casein and in calcium and the half

dilution brings it approximately into the soft curd range. But dilution of the clotting constituents need not necessarily be with water for the addition of any other non-clotting factor diminishes the percentage composition of clotting constituents. Therefore the addition of milk modifiers must be included as diluents of the clotting constituents and thus contribute somewhat to the formation of soft curds. Slight dilution, less than 10 per cent., produces too small an effect on the curd tension to be significant. In infant feeding practice it is a useless procedure.

TABLE 2.

WATER DILUTION AND CURD TENSION.

MILK PER CENT.	CURD TENSION GM.
100	120
90	80
80	65
70	50
60	40
50	25
40	20
30	10
20	0
10	5

(C) The effect of heating on the curd tension of milk

Heating alters the clotting constituents of milk and consequently the character of the curd. The temperature effect was determined, maintaining the time of heating constant according to previous procedures. Figure 5 presents the average temperature curve from 20° to 100° C. There is a sharp maximum at a little over 40° in the curd tension determination with definite falls in the tension at both lower and higher temperatures than 40° C. In other words a slight rise of temperature of milk to body heat actually increases the curd tension while subsequent heating diminishes it. This is significant in infant digestion. On ingestion of raw milk at room temperature raised to body temperature within the infant's stomach the curd tension of milk is increased beyond its initial value. This temperature curve for curd tension corresponds to that for clotting time determinations of milk. In both there is a maximum at about 40° C. with a gradual diminution on either side of this transition temperature. Apparently clotting time varies inversely with curd tension for optimum clotting at body temperature parallels the maximum curd tension of milk.

But the time of heating is as significant as is the temperature. Experiments were therefore set up to determine the effect of heating milk at 60° C. for varying lengths of time. Figure 5 shows a definite drop in the curd tension on maintaining milk for the initial length of time at 60° C. Increase in the duration of heating at this temperature produced gradually diminish-

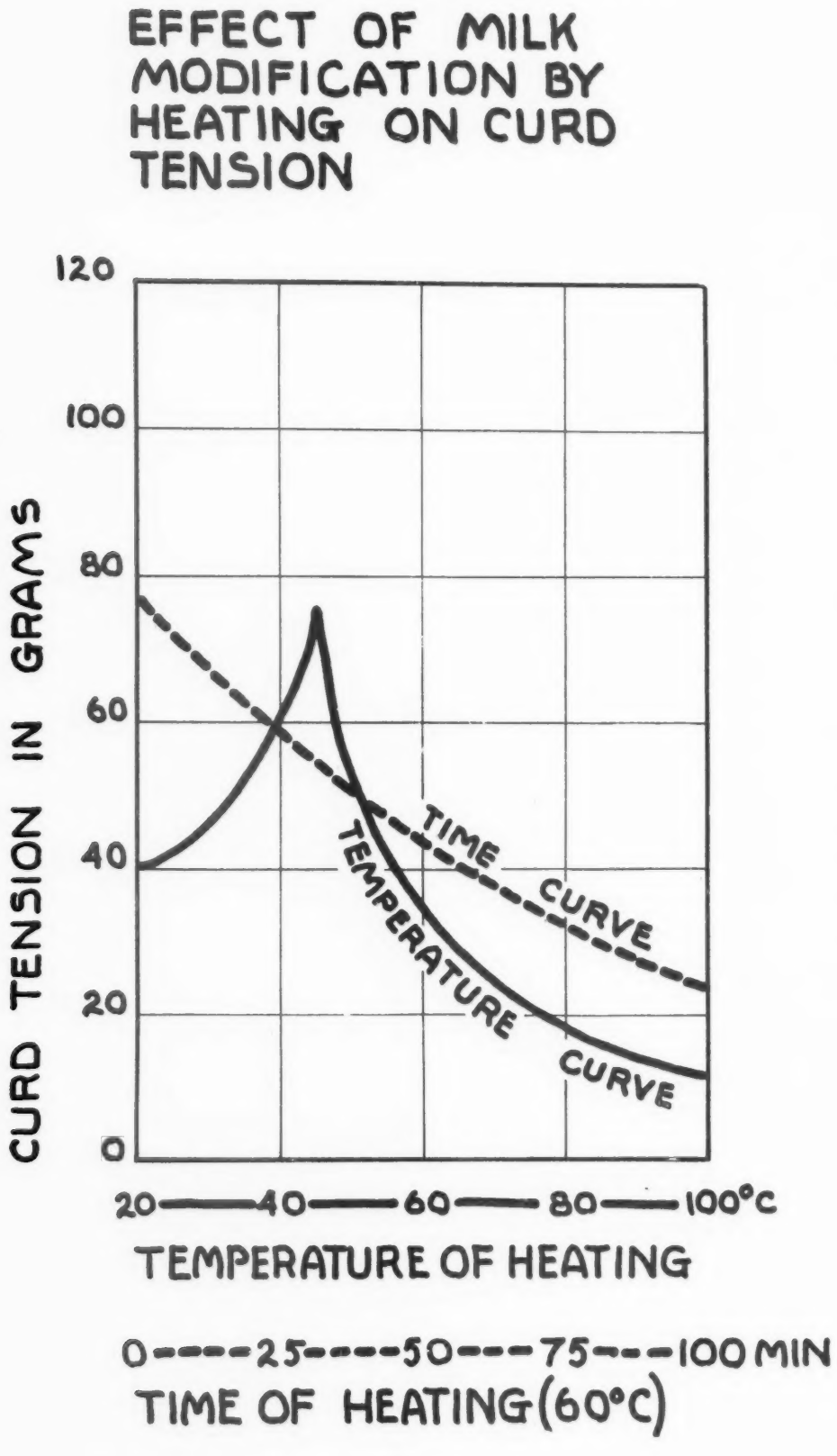
EFFECT OF MILK MODIFICATION BY HEATING ON CURD TENSION
120
100
80
60
40
20
0
CURD TENSION IN GRAMS
TIME CURVE
TEMPERATURE CURVE
20—40—60—80—100°C
TEMPERATURE OF HEATING
0----25----50---75---100 MIN
TIME OF HEATING (60°C)

FIG. 5.

ing effects on the curd tension. The higher the temperature of heating the more marked is the initial drop in the curd tension after the first few minutes. On boiling milk there is little advantage in prolonging the procedure beyond five minutes. Generally, however, the duration of heating at a constant temperature has much less effect upon the character of the curd than the degree of heating for a definite time.

Heat changes the physico-chemical behaviour of milk. The calcium caseinate is denatured and hydrolyzed until finally there is an association of the molecules to form larger aggregates. The higher the temperature the greater the amount of water bound by the caseinate until elevated temperatures are reached when the colloid states are reversed. Initially the caseinate is dispersed in water as a dispersion medium. Upon hydration and aggregation of these large molecules the viscous caseinate separates slowly in the presence of substances which tend to keep it dispersed and so that it becomes the dispersion medium for water as the dispersed phase. The curd shows the characteristics of a gel which is identical with a soft curd. Without considering the simultaneous chemical changes involved in heating milk this hydration phenomenon results in a thickening prior to clotting. It is due to a release of the caseinate or paracaseinate from its combined state with calcium. Both casein and paracasein molecules then swell to capacity, a condition conducive to soft curd formation.

TABLE 3.

EFFECT OF HEATING OF HARD CURD MILK ON THE CURD TENSION.

TEMPERATURE OF HEATING °C.	CURD TENSION GM.	CLOTTING TIME MINUTES	TIME OF HEATING MINUTES	CURD TENSION GM.
20	40	20	Control	75
30	50	12	10	60
40	60	8	20	55
50	55	13	30	50
60	35	18	40	48
70	24	25	50	45
80	18	30	60	40
90	15	35	70	35
100	13	42	80	32
			90	30
			100	30

(D) The effect of hydrogen ion concentration on the curd tension of milk

Acid and alkali modify the course of milk coagulation and the character of the curd[4]. The curd tension at each pH level from 3 to 9 was determined for pasteurized milk. To 100 c.c. a mixture of 0·14 N-hydrochloric acid and 0·1094 N-sodium hydroxide was added in a fine stream by means of a burette, the mixture rotated constantly to prevent any local excess of reagent and the curd tension then determined as in the preceding tests. A

condensed curve of averages is plotted in figure 6 representing the average curd tension of milk at various pH levels combined from nine complete titrations.

Pasteurized milk shows a maximum curd tension at about pH 6·0. On the acid side of this maximum the rapid decrease in curd tension with increased acidity is caused by the removal of casein from colloid solutions

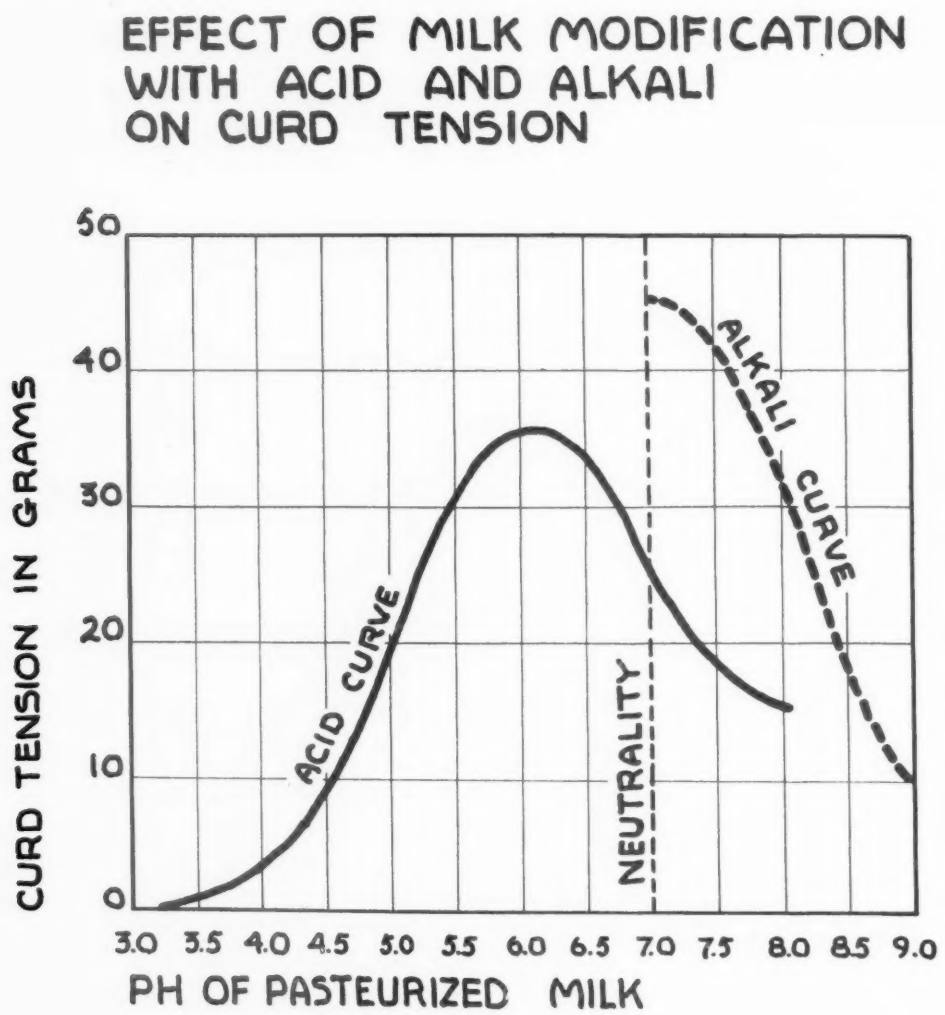

FIG. 6.

by the precipitation of acid which leaves less and less of the protein to react with the pepsin. The curd tension on the alkali side of the maximum is due chiefly to the inactivation of the pepsin by hydroxions. Upon addition to milk modifiers, crystalloids (sugars) or colloids (powdered banana, gelatin), the maximum inflection point is displayed by a flattened zone from about 5·5 to about 6·5 and zero curd tension is reached at less acid reaction than does milk alone. A zero curd tension with modified milk is also reached on the alkaline side of the isoelectric point of casein. No

attempt was made to extend these curves beyond 8·5 since the quinhydrone electrode ceases to give reliable results beyond this range.

The hydrochloric acid used in these titration experiments with pasteurized milk produced a very soft curd near the isoelectric zone of casein. Its use in the modification of milk is less frequent in this country than on the continent. The character of the curd was compared with other acids. The curd from phosphoric is comparable to that of hydrochloric, acetic is slightly firmer, citric is very firm and so is the lactic acid curd produced naturally or artificially. Not only is there a difference in the casein curd formed with different acids but also with different milks. Evaporated milk gives soft spongy curds, powdered milk (spray process) compact curds and pasteurized milk intermediate between them. When powdered milk is roller processed the curd obtained is soft.

TABLE 4.

pH AND CURD TENSION.

Acid pH	Curd tension (average) gm.	Alkali pH	Curd tension (average) gm.
3·0	0	7·0	46
3·5	2	7·5	42
4·0	5	8·0	32
4·5	9	8·5	17
5·0	18	9·0	10
5·5	30		
6·0	35		
6·5	35		
7·0	26		

TABLE 5.

Properties of milk curd.

Rennet coagulation	Acid coagulation
Calcium paracaseinate formed	Casein formed
Elastic, retractile	Inelastic, non-retractile
Spongy, plastic	Floccular, sticky
Curd tension high	Curd tension low
pH zone 6–7	pH zone 4–5
Mineral content high	Mineral content low
Whey exudation great	Whey exudation slight
Serum clear	Serum cloudy

(E) Effect of milk modification with colloids on curd tension

The character of the curd upon addition to milk of banana, gelatin and gruels respectively has been determined. The colloid was weighed into a curd tension jar, the milk added and allowed to stand at room temperature temperature for ten minues. The jar was then placed in a water bath at 60° C. with occasional stirring until completely dispersed. The container was then transferred to a water bath at 37° C. and the curd tension measured at equilibrium. The results of this study are given in table 6, the curd tension values being the average of duplicate determinations.

Whatever the milks used, be it hard or soft curd, the curd tension is lowered by the addition of any of the colloidal modifiers used. Each represented a characteristic colloidal state, barley a hydrophobe, banana intermediate between hydrophobe and hydrophile and gelatin a hydrophile colloid. The diminution in curd tension parallels this order of degree of hydration of the colloid in milk. Assuming that a curd tension of 30 gm. or less represents a soft curd milk, 90 per cent. (51) yielded soft curd milk upon addition of 3 per cent. gelatin, 5 per cent. banana, 8 per cent. barley. The curd tension of the original milks having been from 40 to 60 gm. The most pronounced lowering occurred in the milk which had the highest curd tension. The curves (fig. 7) represent the average curd tension of the milks with a progressive softening of the casein upon increasing the amounts of colloid. An addition effect of adding a colloid to milk is to make it more acid by 0·1 to 0·3 pH units. From the curve in figure 6 such a change in pH produces no lowering of curd tension. The decrease in curd tension from 20 to 60 per cent. of the original values is therefore due to protective action of the colloidal modifier of milk.

TABLE 6.

COLLOIDS AND CURD TENSION.

BARLEY PER CENT.	CURD TENSION GM.	BANANA PER CENT.	CURD TENSION GM.	GELATIN PER CENT.	CURD TENSION GM.
0	45	0	42	0	40
1	42	1	39	1	32
2	39	2	36	2	27
3	37	3	33	3	23
4	35	4	30	4	21
5	33	5	28	5	18
6	32	6	27	6	17
7	31	7	26	7	15
8	31	8	24	8	14
9	31	9	22	9	13
10	30	10	21	10	12

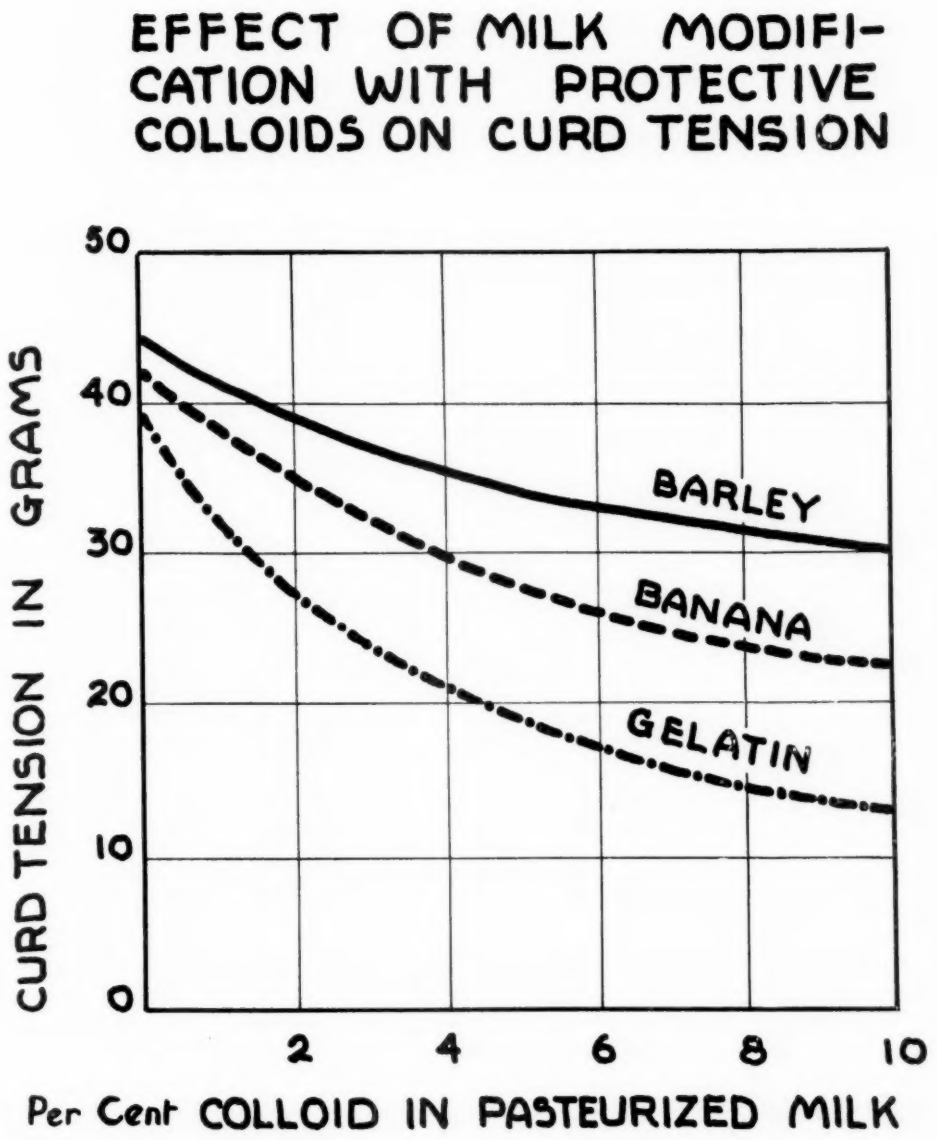
EFFECT OF MILK MODIFICATION WITH PROTECTIVE COLLOIDS ON CURD TENSION
CURD TENSION IN GRAMS
50
40
30
20
10
0
BARLEY
BANANA
GELATIN
2
4
6
8
10
Per Cent COLLOID IN PASTEURIZED MILK

FIG. 7.

TABLE 7.

EFFECT OF COLLOID ON THE CURD TENSION OF MILK.

	AVERAGE CURD TENSION IN GRAMMES.						
	PERCENTAGE OF COLLOID.						
	0	5	6	7	8	9	10
Barley	0	5	6	7	8	9	10
Banana	0	3	4	5	6	7	8
Gelatin	0	1	2	3	4	5	6
	CERTIFIED MILK.						
	36						
	27	28	25				
	21	19	24	17			
	41	38	35	33	35		
	37	31	31	27	23	25	
	53	45	39	25	23	27	21
	36	24	15	18	19	17	14
	SOFT CURD MILK.						
	23					14	
	26					11	
	18	15	15	17	11		
	30	28	28	25	20		
	35	23	23	21	21	16	
	32	31	26	21	19	14	16
	23	17	17	14	14	15	13
	PASTEURIZED MILK.						
	30		29				
	21			11			
	28			21			
	32			31			
	34				29		
	50					20	
	30						19
	34	37		45			
	35		19		16		
	38					22	
	29						19
	23	22	14	14			
	30				17		
	39	33	27		15		12
	27	19	21	19	16		19
	32	30	27	26	25		20

FIG. 8.—Effect of cow's milk modifications on the character of the curd.

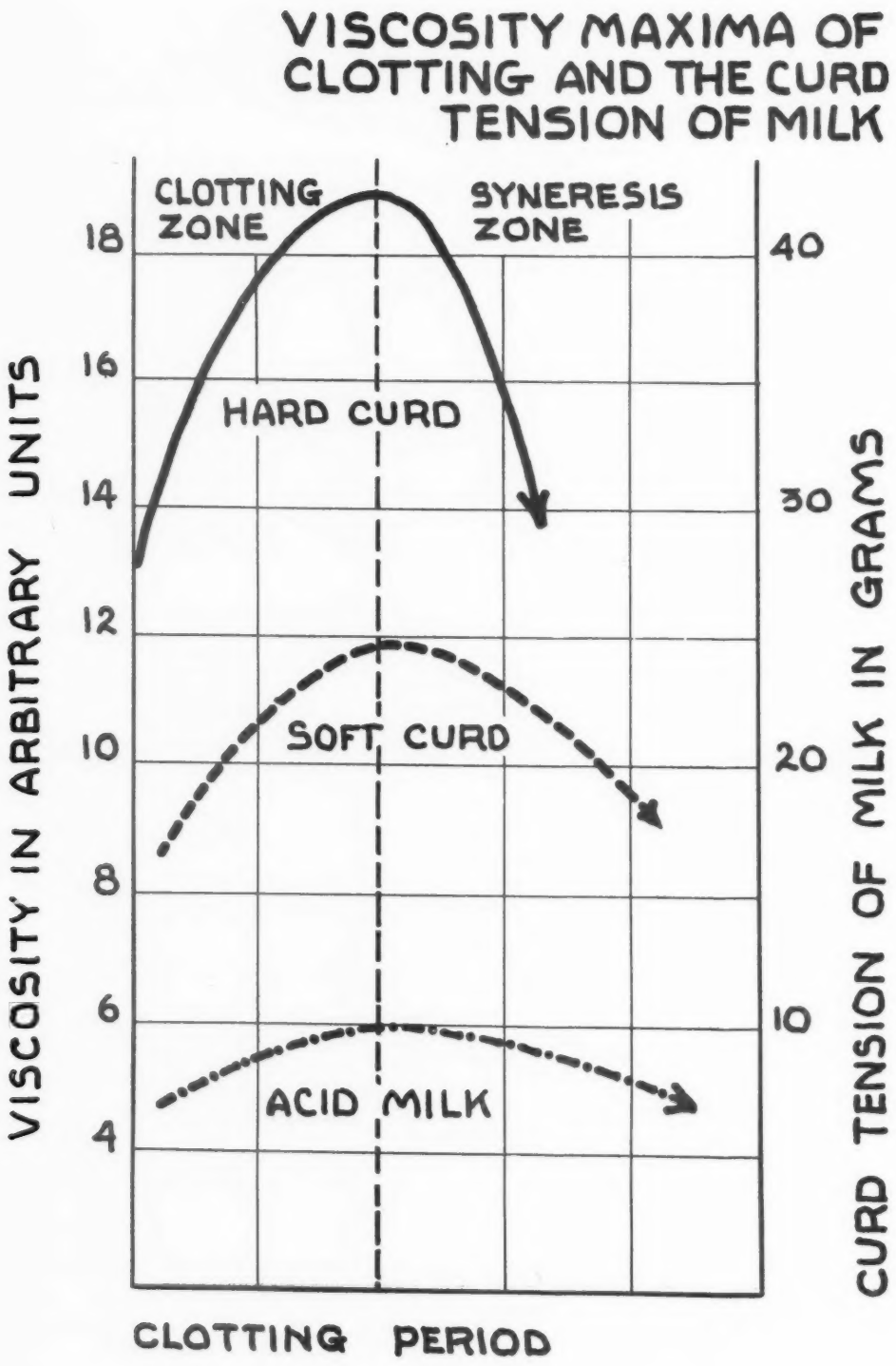
VISCOSITY MAXIMA OF CLOTTING AND THE CURD TENSION OF MILK
CLOTTING ZONE
SYNERESIS ZONE
HARD CURD
SOFT CURD
ACID MILK
VISCOSITY IN ARBITRARY UNITS
CURD TENSION OF MILK IN GRAMS
CLOTTING PERIOD
18
16
14
12
10
8
6
4
40
30
20
10

FIG. 9.

TABLE 8.

EFFECT OF GELATIN ON THE pH AND CURD TENSION OF MILK.

MILK ALONE		MILK—5 PER CENT. OF GELATIN		LOWERING OF CURD TENSION
pH	CURD TENSION GM.	pH	CURD TENSION GM.	PER CENT.
6·59	43	6·45	20	54
6·58	20	6·32	12	40
6·58	19	6·36	15	21
6·54	32	6·30	12	63
6·54	20	6·33	16	20
5·77	36	5·46	16	56

(F) Effects of various milk modifications on the swelling of the clot

Every change in milk affects its physical behaviour. This changes the character of the curd. On modifying milk according to previous procedures the clot was obtained, centrifugalized and dried and the volume determined by displacement. Figure 9 shows the relative increase in volume with modification by heat, dilution, acidification, alkalinization and colloid additions, in comparison with the clot obtained from unmodified milk. Upon addition of the clotting constituents, rennet, calcium and casein to milk a diminution in volume occurred with the formation of hard compact curds respectively. Apparently clots obtained from clotting constituents in milk below certain percentage composition will swell while those of higher content will lose water and shrink. Between the swelling and shrinking of the clot there is a transitional milk composition which will neither swell nor shrink on coagulation[5].

By an increase in volume is meant, generally speaking, the difference in total volume of all the participants before and after the process. The volume change that occurs when NH_4Cl is dissolved in water is not the difference between the volume of the solution and that of the water but the difference between the volume of the solution on one hand and the combined volumes of water and salt on the other; hence the observation of the increase in volume of a gel immersed in liquid cannot be interpreted by saying that the process of swelling takes place with an increase in volume. The two things to be compared are the swollen gel and the dry gel plus fluid. This comparison leads to the inference that swelling is characterized by a decrease in volume. Fluid is forced into capillary spaces and increase in surface brings about compression of the dispersed phase.

Paracaseinate gels are two phase, three component systems. The solid phase consists of particles or micellae of calcium paracaseinate, some of which is dissolved and some dispersed in the liquid phase. Each micella is a distinct system with an insoluble elastic wall or network containing an internal liquid phase. The paracaseinate anions are not in solution in the strictest sense since they form part of the gel network, the calcium ions

existing in the interstitial solution. The calcium ions are balanced only by the negative electrical charges on the network of paracaseinate. In consequence there is an unequal distribution of all ions between the interstitial solution and the external solution, the total concentration of ions in the gel being always greater than in the main solution. The cations of the calcium paracaseinate tend to diffuse into the external solution and so exert an attraction on the anions which form part of the gel structures. This causes the volume of the gel to increase in direct proportion to the excess of concentration of diffusible ions of the gel over that of the main solution. The greater the proportion of paracaseinate existing in the ionic state the greater the swelling produced.

Shrinking, the converse of swelling, is represented by a phenomenon called syneresis. It appears as a separation of whey squeezed out from the contracting clot. Syneresis is produced by the elastic stress in the micellae of the paracaseinate solution. Elastic stress in the micellae is due to the unusually high concentration of the paracaseinate or other clotting constituents in the internal liquid phase. When they become supersaturated paracaseinate separates out of solution. The force within the micellae which keeps the micellae stretched is therefore diminished. The elastic walls of the micellae contract with the result that the liquid expelled from both

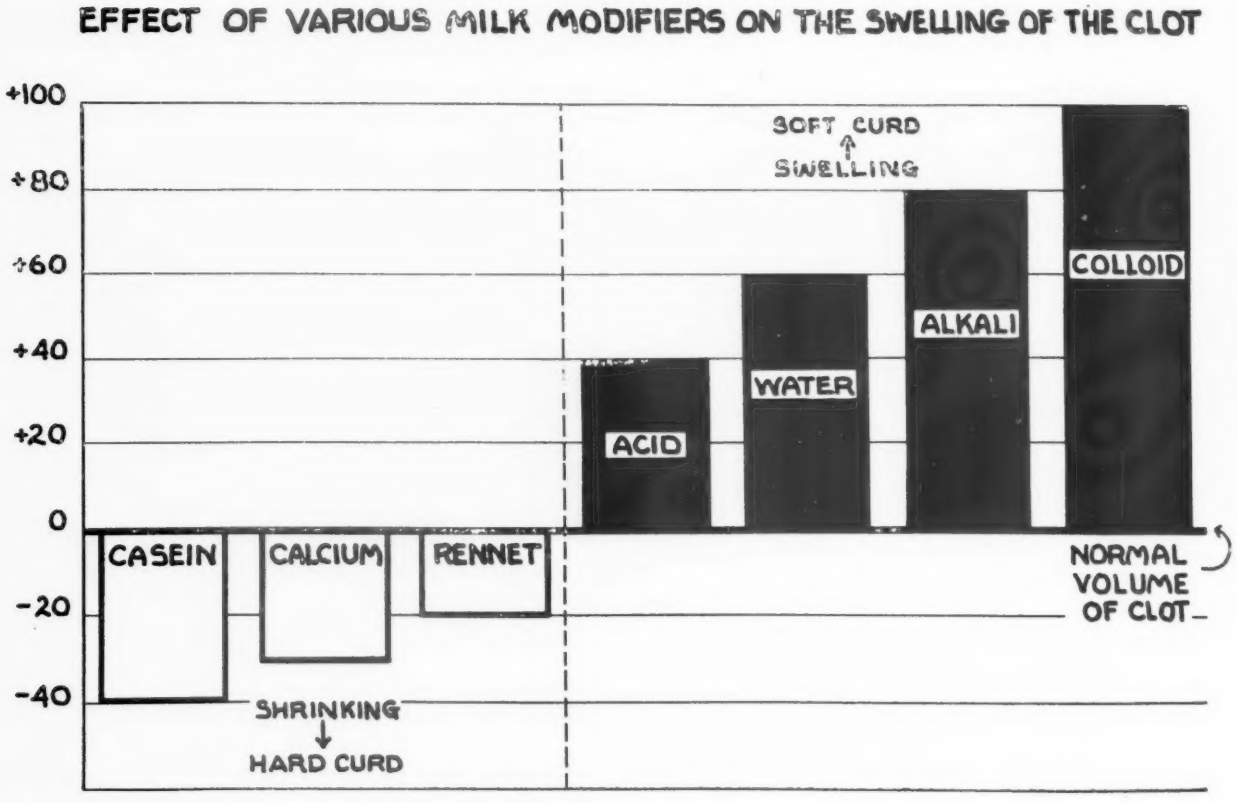

FIG. 10.

micellae and interspaces is syneresis fluid. The size of the particles increases continuously. Several lyophobic portions appear on one and the same particle. These gradually tend to cohere thus necessitating contraction of the gel and expulsion of the fluid in the pores.

(G) The relation between viscosity and curd tension of milk

The course of milk coagulation was followed for viscosity measurement in a previous communication. It was observed that the viscosity curve was autocatalytic. After a latent period of clotting wherein viscosity changes were slight, a sudden and marked rise in viscosity characterized the clotting stage of milk. Each modification of milk altered this viscosity maxima. This was particularly observed in measuring the viscosity maxima of milks of various curd tensions. Figure 10 shows that hard curd milk is 50 per cent. higher in viscosity at its maximum than is soft curd milk. There is also a striking difference in the duration and degree of contraction of the clot, hard curd squeezing out the whey more rapidly and more effectively than does the soft curd. The maximum so attained is thus a function of the concentration of the clotting constituents, casein, calcium and rennet. The factors that tend to swell the clot produce low viscosity maxima as is illustrated in figure 10 with acid milk. Very slight changes in the curd tension of milk suffice to produce marked effects in the viscosity maxima attained during the clotting of milk.

Summary

1. The curd tension of milk is determined by the concentration of the clotting constituents, casein, calcium and rennet. A casein content of 2·5 per cent. delimits soft curd milk, a slight rise in the concentration increasing markedly the curd tension. A calcium content of 0·125 per cent. delimits soft curd milk, increasing concentrations raising the curd tension but moderately. The rennet concentrations have the least effect upon the tensile strength of the curd. Curd tension generally varies inversely with the clotting time of milk.

2. The curd tension of milk diminishes rapidly with dilution. Fifty per cent. dilution delimits soft curd milk. Milk modifiers diminish the curd tension as diluents of the clotting constituents.

3. Heating alters the curd tension. A rise in the temperature of milk to about 40° C. actually increases curd tension while subsequent heating diminishes it with a maximum at body heat. The time of heating at various temperatures likewise modifies the character of the curd, the diminution in curd tension being more marked the higher the temperature of heating.

4. The curd tension in a function of the hydrogen ion concentration of milk with a maximum at about pH 6·0. On both the acid and alkaline sides of this maximum there is a marked diminution in curd tension. Additions of milk modifiers displace this maximum to a flattened zone extending from about pH 5·5 to 6·5. Each acid produces a characteristic

curd at the same pH in the following order, hydrochloric, phosphoric, acetic, lactic, citric, hydrochloric producing the softest curd and citric the firmest.

5. Rennet clotting is characterized by the formation of calcium paracaseinate, retractility, plasticity, high curd tension, pH zone around 6·5, high mineral content, exudation of clear whey. Acid coagulation is characterized by the formation of casein, non-retractility, floccular, low curd tension, pH zone around 4·5, low mineral content, slight but cloudy whey formation.

6. Colloidal milk modifiers diminish the curd tension progressively in the following order, sugars, barley, banana, gelatin.

7. Milk modifiers alter the volume of the clot. Heat, dilution, acidification, alkalinization and colloids produce swelling of the clot while additions of the clotting constituents, casein, calcium and rennet produce a shrinking of the clot. Swelling of the clot is conducive to soft curd formation and shrinking to hard curd.

8. Hard curd milk shows a viscosity 50 per cent. higher at this maximum than soft curd milk while acid milk shows the viscosity maximum 50 per cent. lower than that of soft curd milk.

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THE SIGNIFICANCE OF PLASMA PHOSPHATASE IN THE DIAGNOSIS AND PROGNOSIS OF RICKETS

BY

NOAH MORRIS, MARY M. STEVENSON, OLIVE D. PEDEN AND JEAN M. D. SMALL.

(From the Department of Paediatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow, and Public Health Department, Stobhill Hospital, Glasgow.)

Although it is true that ordinary clinical examination suffices for the diagnosis of moderate degrees of rickets, most workers would agree that something more is necessary for the detection of milder forms of the disease, when the metabolic disturbances are not sufficiently great or have not continued long enough to produce clinical manifestations. For this purpose skiagrams have been used to great advantage both in practice and as an instrument of research. There are, however, several drawbacks associated with their employment. In the mildest forms of the disease the interpretation of the skiagrams is a matter of considerable difficulty; indeed, it may be classified as a subjective test. In the second place it is not possible in many cases to determine whether any healing is taking place until a series of at least three skiagrams taken at weekly intervals is available. For this reason it is difficult to estimate by x-rays alone, the initial stages of healing. Undoubtedly the most accurate method of determining the presence or absence of the rachitic process and its severity is by estimating the actual retention of minerals. Unfortunately this is laborious, time-consuming and quite unsuited for general use in making prolonged studies on a series of patients. Resort has therefore been made to chemical examination of the blood. The serum calcium does not alter markedly in uncomplicated rickets but a reduction of the inorganic phosphorus has long been used as a valuable indication of the presence of rickets. This latter test suffers from some of the defects associated with x-ray examination, in that there is usually little change in the level of serum phosphorus for two to three weeks after the start of antirachitic therapy, whereas metabolic studies have shown that within one week, administration of vitamin D leads to a marked increase in mineral retention.

Freudenberg[1] points out that a low serum phosphorus is not pathognomonic of rickets since it may occur in pneumonia and other acute infections, muscular dystrophies, myxoedema and coeliac disease. Furthermore, Hess[2] and others[3, 4] have shown that sometimes the phosphorus content of the serum may be normal even when there are definite clinical

manifestations of active rickets. Marfan[5] also states that the decrease in serum phosphorus cannot be regarded as a regular feature of rickets. It certainly is within the experience of most workers that occasionally the serum phosphorus is within normal limits although the clinical and x-ray findings indicate an active stage of the disease. Bodansky and Jaffe[6] found that while serum phosphorus is generally low in untreated rickets, it rapidly responds to treatment, so that when small amounts of a vitamin D preparation have been given for a short time a relatively high value for serum phosphorus does not give a reliable indication of the stage or extent of healing. This has also been observed by the present writers on several occasions. Conversely it has been shown that serum phosphorus may remain low although signs of healing are present both on clinical and x-ray examinations.

The product of the calcium and phosphorus values of the serum has for some time been accepted by many as a valuable index of the rachitic process. A product above forty indicates healing and one below thirty an active stage. But its significance has been disputed by Hess[2] who obtained products above forty without signs of healing: on several occasions we have had the same experience.

Since Robison's work was first applied to clinical conditions, variations of the plasma phosphatase in rickets have been studied with a view to utilizing its estimation as a means of determining the presence and stage of the rachitic process.

Kay[7] found that in various types of human rickets the plasma phosphatase was increased. Smith and Maizels[8] stated that in rachitic infants the plasma phosphatase which prior to treatment was about two-and-a-half times the normal average, decreased gradually after the commencement of antirachitic therapy, arriving within normal limits only when healing was complete. Stearns and Warweg[9], however, found that the plasma phosphatase was still above normal limits even when complete healing was shown in the skiagrams. Bodansky and Jaffe[6] obtained in rickets much higher values for plasma phosphatase than did Smith and Maizels[8]: this they attributed to the fact that their patients were negro infants on whom sunlight would have less prophylactic effect than on white children. Smith[10] has stated that the plasma phosphatase is probably a much more sensitive and accurate index of abnormal bone metabolism than is either serum calcium or phosphorus.

The purpose of this communication is an attempt to assess the value of plasma phosphatase as a diagnostic test for rickets and also as a means of determining the presence and rate of healing. The results are based on the examination of 506 infants and children in the first two years of life who either had manifest rickets or might possibly have been suffering from the effects of vitamin D insufficiency. They were all in-patients in the medical wards of the Royal Hospital for Sick Children, Glasgow, or the children's wards of Stobhill Hospital. The method employed for estimating phosphatase was that devised by Jenner and Kay[11]. Using this method we have found in a series of healthy infants of the first two years of life that the limits for plasma phosphatase fell between 3·4 and 10·5 units with an average of 6·92 and any value above 11·0 has been considered to be higher than normal.

Plasma phosphatase in the presence of clinical evidence of rickets

The first question to be answered is whether clinical and x-ray signs of rickets are always accompanied by an increased value for plasma phosphatase or not. Of 270 cases with positive clinical or x-ray findings, 227 (84·1 per cent.) showed an increased value for phosphatase, while in 43 (15·9 per cent.) the figures were within normal limits (table 1). In only

TABLE 1.

A. Incidence of high plasma phosphatase, low serum phosphorus, and low calcium-phosphorus product in cases with clinical or radiographic signs of rickets.

	Plasma phosphatase		Serum phosphorus		Calcium-phosphorus products	
	High	Normal	Low	Normal	Low	Normal
No. of cases	227	43	174	82	175	39
Percentage	84·1	15·9	68·0	32·0	81·7	18·3

B. Incidence of clinical or radiographic signs of rickets in cases with high plasma phosphatase, low serum phosphorus and low calcium-phosphorus product.

	High plasma phosphatase		Low serum phosphorus		Low calcium-phosphorus product	
	Signs	No signs	Signs	No signs	Signs	No signs
No. of cases	227	101	174	127	175	128
Percentage	69·9	30·1	57·8	42·2	57·7	42·3

five of the latter group of 43 was the rickets at all marked: in one of these the estimation of the phosphatase was repeated three times within ten days with practically identical results. It would appear, therefore, that while in the majority of cases of rickets there is an increase of plasma phosphatase there is a small group in which such an increase does not occur.

In 101 cases an increased value for phosphatase was obtained without either clinical or x-ray signs of rickets. Of these, 59 had low values for the serum phosphorus or the calcium phosphorus product, suggesting that a rachitic process might have been present. Opportunity was afforded of re-examining five of the 42 patients with normal values for serum phosphorus some months later after the infants had been sent home but had not been receiving regular antirachitic therapy owing to the negligence of the parents. In all, definite signs of rickets were present (table 2). This tempts the

TABLE 2.

Name	Date	Clin.	X-ray	Phospha-tase, units	Ca mgm. per cent.	P. mgm. per cent.	Ca × P.
W. P.	2. 5.35	–	–	18·6	9·4	4·8	45·1
	26. 2.36	+	+	15·0	9·6	3·1	29·8
J. McD.	25. 4.35	–	–	13.5	9·0	4·5	40·5
	20.10.35	+	+	9·5	9·4	4·2	39·5
R. G.	28.10.35	–	–	18·8	9·8	–	–
	7. 7.36	+	+	14·5	9·4	5·6	52·6
J. McG.	31.10.35	–	–	15·0	9·8	4·1	40·2
	8. 7.36	+	+	10·8	9·5	4·7	44·7
W. R.	28.10.35	–	–	16·0	9·3	4·6	42·8
	24. 7.36	+	+	15·4	9·6	3·5	33·6

suggestion that a high plasma phosphatase in a child of an age prone to rickets and without other bone disease may be an earlier manifestation of a rachitic state than that provided by ordinary clinical or x-ray examination.

It is also evident from the data in table 1 that a high plasma phosphatase is more frequently associated with clinical evidence of rickets than is a reduced serum phosphorus. Of 256 cases with rickets, only 68 per cent. (174) had a low serum phosphorus, while 84·1 per cent. had an increased value for plasma phosphatase. The relationship between a reduced value for the calcium-phosphorus product and clinical evidence of rickets resembles that found with phosphatase: 81·7 per cent. of 175 patients had a low product. It would appear also that in the first two years of life the chances of a high plasma phosphatase being associated with rickets are greater than those of a low serum phosphorus or low product. Of 328 cases with high phosphatase 69·9 per cent. (227) had rickets, while of 301 with low phosphorus only 57·8 per cent. (174) and of 303 with low product only 57·7 per cent. (175) had any clinical or x-ray evidence of rickets.

From these figures the conclusion is justified that as far as blood examination is concerned plasma phosphatase is probably the most delicate test of rickets. Nevertheless although the correlation is close it would be unwise to use the phosphatase value alone as conclusive evidence of the presence or absence of rickets.

Height of phosphatase and intensity of the rachitic process

The highest value obtained in the series was 37·2 units, about five times the normal average. This is relatively not as high a figure as many of those reported by Bodansky and Jaffe[6] but none of the present series of patients could be classed as a very severe case of rickets. Table 3 shows the distribution of phosphatase values. Owing to the practical impossibility of devising an accurate test for estimating moderate differences in the degree of rachitic involvement in the human subject it is difficult to compare one patient with another unless there are marked differences in the clinical and x-ray findings. A general survey of the series indicates that in a general way the height

TABLE 3.

DISTRIBUTION OF PHOSPHATASE VALUES.

Phosphatase, units	2·6 – 6·0	6·1 – 11·0	11·1 – 15·0	15·1 – 20·0	20·1 – 25·0	25·1 – 30·0	Above 30·1
No. of cases with no clin. or X-ray evidence of rickets.	27 (11·4 per cent.)	108 (45·8 per cent.)	64 (27·1 per cent.)	37 (15·7 per cent.)	0	0	0
No. of cases with clin. or X-ray evidence of rickets.	10 (3·7 per cent.)	33 (12·2 per cent.)	96 (35·6 per cent.)	83 (30·8 per cent.)	33 (12·2 per cent.)	13 (4·8 per cent.)	2 (0·7 per cent.)

of the phosphatase ran parallel with the degree of rickets as judged by clinical evidence. This correlation is not a close one and cases with mild rickets have been observed with a much higher phosphatase than was found in other patients with more marked signs of rickets (table 4). In individual

TABLE 4.

EXAMPLES OF INCONSISTENCY BETWEEN HEIGHT OF PLASMA POSPHATASE AND SEVERITY OF CLINICAL FINDINGS IN RICKETS.

NAME	CLIN.	X-RAY	PHOSPHATASE, UNITS	Ca MGM. PER CENT.	P. MGM. PER CENT.	Ca × P.
W. C.	+	N	22·8	9·9	4·5	44·6
R. F.	+	N	26·7	9·0	3·6	35·3
J. M.	+	N	24·7	—	4·8	—
I. A.	+++	+ +	16·1	10·9	3·1	33·8
R. D.	+++	+ +	17·9	—	2·1	—
H. McL.	+++	+ +	16·0	—	2·9	—

TABLE 5.

PLASMA PHOSPHATASE AND SERUM PHOSPHORUS IN RICKETS.

	NO. OF CASES WITHOUT CONVULSIONS. SERUM P.		NO. OF CASES WITH CONVULSIONS. SERUM P.	
	LOW*	NORMAL	LOW*	NORMAL
High phosphatase	143	73	35	33
Normal phosphatase	31	9	17	19

* Below 4 mgm. per cent.

cases, however, the intensity of the rachitic processes can be measured by making observations during the stage of healing when it is found that the phosphatase is reduced as calcification returns to normal. It is evident that the height of the plasma phosphatase cannot be used as a means of comparing the severity of rickets in different patients, although as will be more fully discussed later it is of value in the estimation of the recovery process in the same patient.

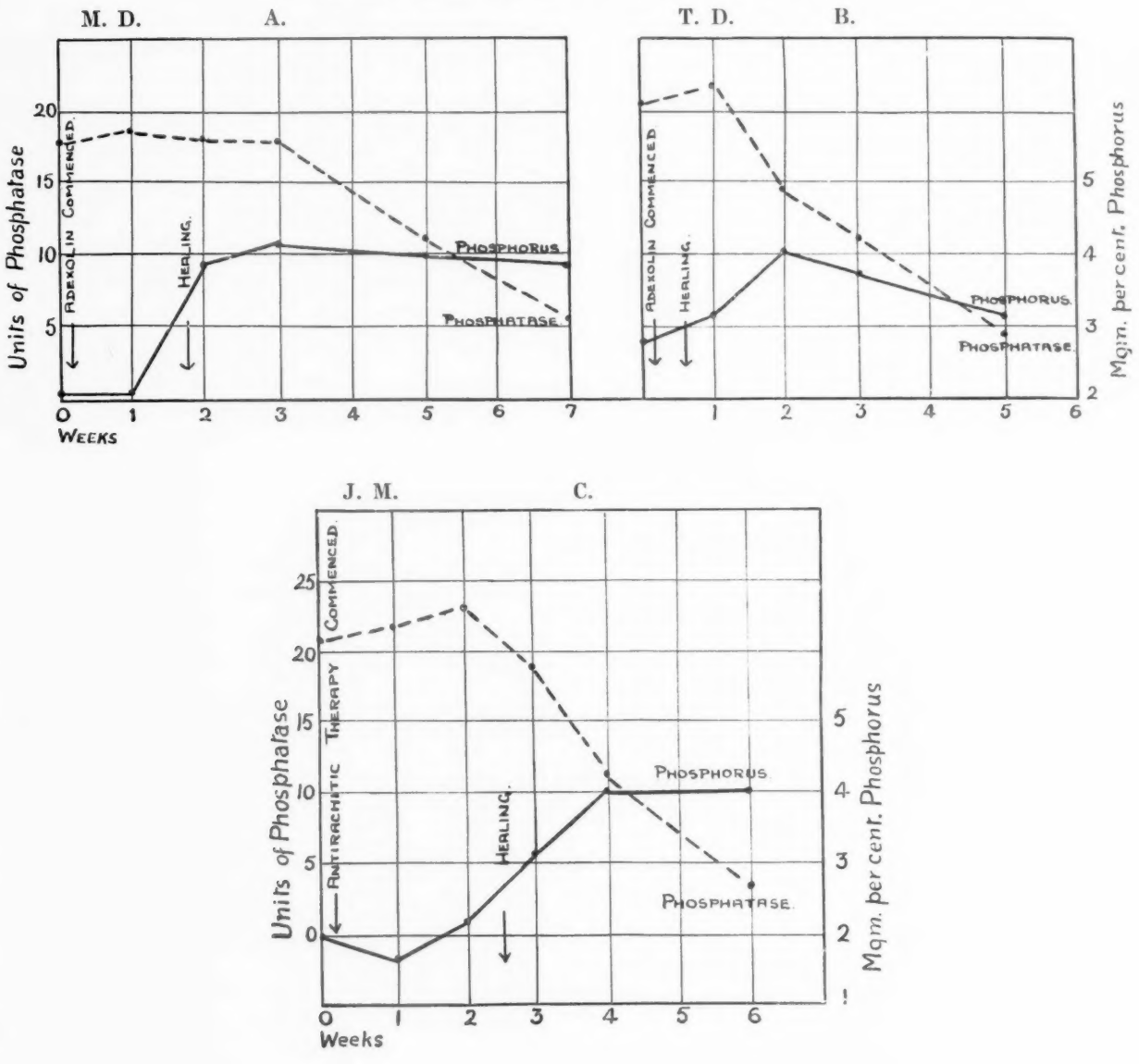
Relationship between the phosphorus and the phosphatase of the blood

From table 5 it will be seen that of 174 cases of uncomplicated rickets with low serum phosphorus (below 4·0 mgm. per cent.) 143 (82·2 per cent.) had a high phosphatase, while of 216 cases with a high phosphatase, 143 (66·2 per cent.) had a low serum phosphorus. It would appear therefore that in the absence of convulsions, a low value for serum phosphorus is generally accompanied by a high plasma phosphatase. The association is not so close in cases of convulsions since in this group, only 35 (67·3 per cent.) of the 52 patients with low phosphorus had a high phosphatase, while of 68 with high phosphatase, 33 (48·6 per cent.) had a normal phosphorus. The coefficient of correlation between the phosphorus and phosphatase values was determined in the whole series of cases and found to be low, only 68·7 per cent. of the cases with low phosphorus having high

phosphatase. In individual rachitic patients simultaneous determinations of phosphatase and phosphorus show in some cases a considerable degree of association between the two values (fig. 1c, 3a). These results indicate

FIG. 1.

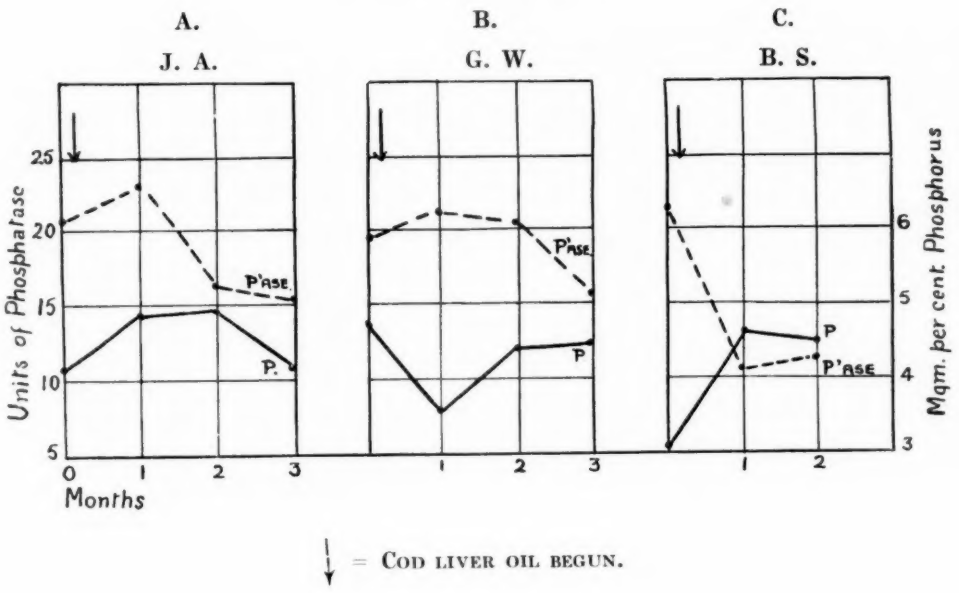
EFFECT OF ADEXOLIN 30 MINIMS THREE TIMES A DAY.



that the relationship between phosphatase and phosphorus is probably no more than a tendency to move in opposite directions. This is by no means a general rule: thus when tetany is present the serum phosphorus is frequently high and often a preliminary reduction occurs shortly after the commencement of antirachitic therapy.

FIG. 2.

EFFECT OF COD LIVER OIL.



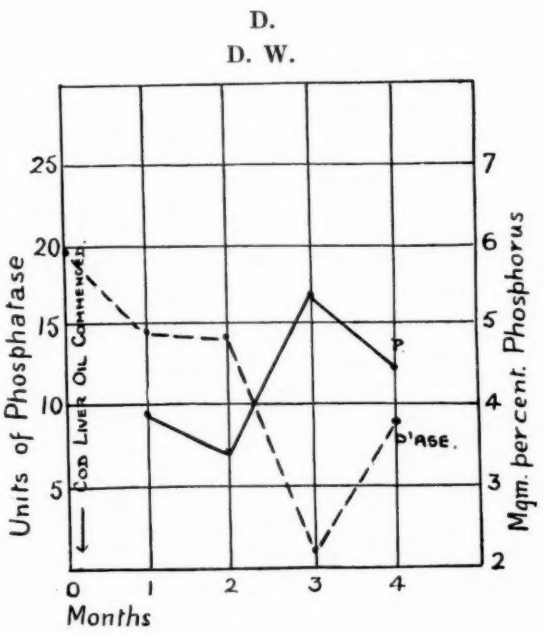
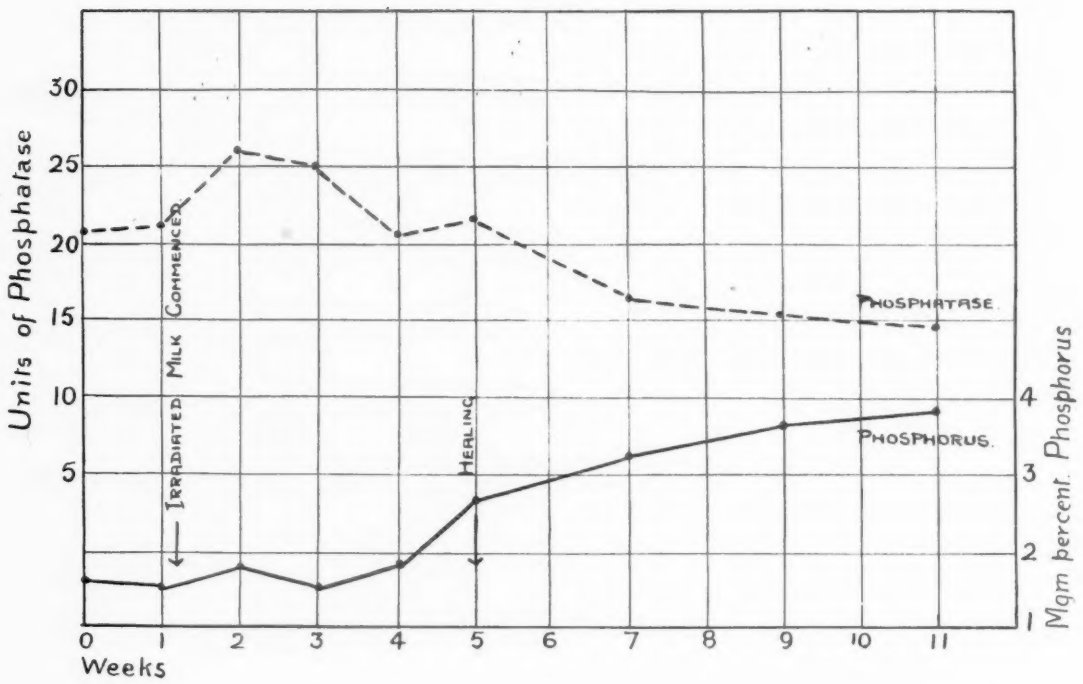


FIG. 3.

EFFECT OF IRRADIATED MILK.

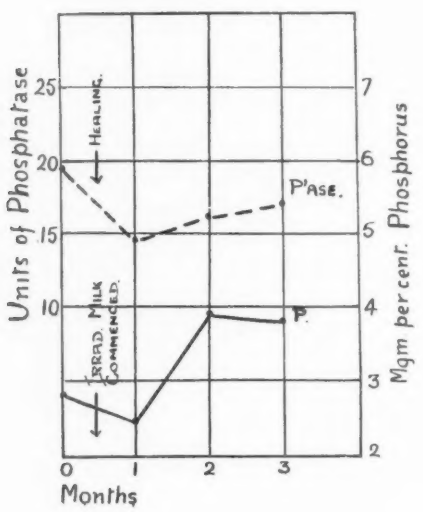
A.

I. N.



B.

D. B.



Phosphatase and calcium-phosphorus product

The association between these two values was also found to be close. Of 130 cases with product below 40, uncomplicated by convulsions, 109 (83·8 per cent.) had an increased phosphatase, while of 139 with a high phosphatase only 30 (21·6 per cent.) had a normal product (table 6). In

TABLE 6.

PLASMA PHOSPHATASE AND CALCIUM-PHOSPHORUS PRODUCT IN RICKETS.

	No. of cases without convulsions. Ca × P.		No. of cases with convulsions. Ca × P.	
	Low*	Normal	Low*	Normal
High phosphatase	109	30	45	14
Normal phosphatase	21	3	19	15

* Below 40.

the cases with convulsions there appeared to be a closer connection between phosphatase and the calcium phosphorus product than between phosphatase and phosphorus, due no doubt to the reduction of calcium compensating for the increase in phosphorus which may occur in the convulsions of tetany.

The effect of administration of vitamin D

Several investigators[8, 14] have shown that the administration of vitamin D leads to a fall in the plasma phosphatase value. Fig. 1, 2, 3 show the results obtained in eight cases examined at frequent intervals. Several interesting points are demonstrated. In the first place it is evident that the plasma phosphatase may remain stationary when evidence of healing is obtained on the skiagram and even when the serum phosphorus is on the increase. This supports the view put forward by Bodansky and Jaffe[6] that it is only a rising value for phosphatase which indicates active rickets. These workers state that a solitary high value for plasma phosphatase indicates merely the presence of rickets and not the absence of healing and that in active rickets the phosphatase content is increased. There has been an opportunity of observing the changes in plasma phosphatase in four cases of untreated rickets over periods of one to three weeks. In all four the phosphatase increased in value (table 7) while the

TABLE 7.

SHOWING INCREASE OF PLASMA PHOSPHATASE WITHOUT TREATMENT.

Name	Date	Plasma phosphatase units
J. S.	18. 3.36	16·3
	9. 4.36	29·3
D. McL. ...	20. 3.36	13·2
	24. 3.36	17·0
	14. 4.36	20·4
H. McL. ...	22.11.35	16·8
	29.11.35	21·0
D. B.	30. 1.35	17·7
	11. 2.35	25·5

skiagrams showed evidence of continued activity of the rachitic process. These results provide strong confirmation of Bodansky and Jaffe's view[6].

Secondly, the initiation of antirachitic therapy is occasionally followed by a small but definite rise of the plasma phosphatase which may amount to two units. This is possibly related to the biphasic action of vitamin D pointed out by Hottinger[12] and by Morris, Graham and Ford[13] who showed that shortly after the start of vitamin D administration there may be a diminution of calcium retention even to the extent of a markedly negative balance.

Thirdly, the fall of phosphatase in every case occurred after the appearance of signs of healing on the skiagrams. Unless therefore a stationary value for the phosphatase is taken as evidence of healing, determination of the phosphatase content of plasma is not an earlier criterion of healing than that afforded by skiagrams. The serum phosphorus usually commenced to rise before there was any fall in phosphatase although the converse was found in one case.

Fourthly, it is clear that the greater the dosage of vitamin D the more rapid is the fall of the phosphatase value. Large doses of vitamin D (90 minims of ' adexolin ' daily) led to a fall of the phosphatase value to within normal limits in five weeks. With moderate doses, however, the value did not fall to this level in three months (table 8). This, of course, is in

TABLE 8.

SHOWING VARIATION IN FALL OF PHOSPHATASE WITH DIFFERENT DOSES OF VITAMIN D.

NAME	TREATMENT	WEEKS BEFORE PHOSPHATASE STABILIZED	WEEKS BEFORE PHOSPHATASE WITHIN NORMAL LIMITS
I. N.	Irrad. milk	6	Longer than 10
D. B.	Irrad. milk	—	Longer than 6
J. A.	Cod liver oil ...	11	—
G. W. ...	Cod liver oil ...	13	—
D. W. ...	Cod liver oil ...	6	12
H. McL. ...	Adexolin, 9 minims daily	8	26
J. M.	Adexolin, 90 minims daily	—	5
M. D.	Adexolin, 90 minims daily	—	5
T. D.	Adexolin, 90 minims daily	—	4

accord with general clinical experience that the rate of healing of rickets is dependent on the dosage of vitamin D. The fact that moderate doses of vitamin D may not produce a fall of plasma phosphatase to within normal limits for several months stresses the importance of a long continuance of antirachitic therapy even after clinical recovery is apparently complete, since metabolism cannot be considered to have become normal until phosphatase values have reached normal limits.

Significance of high plasma phosphatase

Andersen[11] believes that a high plasma phosphatase is indicative of an insufficient supply of vitamin D, and support is lent to this conclusion by the finding that administration of vitamin D preparations leads to a diminution of the phosphatase value. This has been observed in a patient who did not show any clinical or x-ray signs of rickets. In this child administration of vitamin D reduced the plasma phosphatase from 17·8 to 14·6 units in two weeks. Nevertheless it must be remembered that since high values are obtained in disturbances of bone metabolism such as Paget's disease and osteitis fibrosa, in which there is no evidence of a vitamin D deficiency, it cannot be considered that a high plasma phosphatase necessarily indicates such a deficiency. The production of phosphatase by bone and other tissues is essentially a manifestation of cellular activity. Indeed it has been pointed out that cells which are functionally inactive such as those of the foetal kidney do not form phosphatase. Thus it would appear that the more active the tissue cells are, the more phosphatase will they produce. Presumably, therefore, the increase in plasma phosphatase in disturbances of bone metabolism indicates an increase in the activity of the bone cells. It has been shown by Bodansky and Jaffe[6] that in healthy children there is a tendency for plasma phophatase to increase at periods when growth is most marked. Per contra Smith [10] has shown that conditions characterized by cessation of growth such as cretinism, scurvy and achondroplasia are associated with low plasma phosphatase, and the present findings in these conditions are similar. Normally an increased activity in bone cells is accompanied by an increased amount of ossification. For this an adequate supply of calcium and phosphorus is required. When the supply available does not satisfy the requirements of the bone cells increasing amounts of phosphatase may be left unused and flow over, as it were, into the plasma. This would occur either because of absolute or relative deficiency in the supply of calcium, phosphorus or vitamin D or alternatively when the cellular activity of osseous tissue reaches such a height that it is impossible with maximal supplies of vitamin D and minerals to satisfy its requirements. In this connection the following observation is of interest.:—

A child aged two years with bony deformities due to old rickets was put on a diet deficient in lime in order to soften the bones and thereafter correct the abnormal curvatures. After a period of two months on this diet the plasma phosphatase showed a definite increase although the child received vitamin D by mouth and was exposed to sunshine (table 9).

TABLE 9.

Effect of low calcium diet (containing vitamin D) on plasma phosphatase.

Name.	Date.	Plasma phosphatase units.
J. A.	19.6.35	14·4
Low calcium diet begun on 22.6.35		
	8.8.35	24·3
Low calcium diet stopped on 10.8.35		
	30.8.35	14·7

This finding supports the view that the plasma phosphatase rises when the supply of available calcium does not meet the demand of the active bone cells. In rickets, as long as more minerals are required for bone formation than are being supplied, the plasma phosphatase will tend to rise, but as soon as the supply becomes sufficient to meet the demand the phosphatase will cease to rise and will ultimately fall to within normal limits. In view of the great calcium depletion of the bones it is not surprising that with the usual doses of vitamin D, a relatively long time is required for the phosphatase to regain the levels observed in health.

It must be emphasized that the conjunction of mineral depletion and grossly inadequate supply of minerals is not alone sufficient to cause an increase of plasma phosphatase. This is well demonstrated in coeliac disease and renal dwarfism. In both of these conditions there is frequently marked osteoporosis with low values for phosphatase. In coeliac disease the association of mineral deficiency with hypovitaminosis D is not sufficient to produce an increase in plasma phosphatase until growth is resumed, i.e., until the bone cells become active, when rickets becomes evident. In renal dwarfism, on the other hand, in which condition there is no deficiency in the vitamin D intake but a marked inability to utilize calcium and phosphorus effectively there is no rise in phosphatase until, as sometimes occurs, a period of growth takes place when rickets appears with a coincident rise in plasma phosphatase. In both conditions it is the inadequacy of the effective mineral supply to the needs of the active bone cells that produces the rise in plasma phosphatase.

The presence of a high plasma phosphatase in the absence of clinical or radiographic evidence of rickets may be attributed to an insufficient supply of calcium to meet the demands of the active bone cells. Whether or not this is termed rickets is a matter of opinion, although it is interesting that five patients who on the first examination had a high phosphatase but no clinical signs of rickets, some nine months later were found to show definite evidence of rickets (table 2). In the first nine months of life an insufficient intake of calcium must seldom occur. It is probable that, if a high plasma phosphatase indicates an inadequate supply of lime to the bone cells, it is almost certainly due at this age to an insufficiency in vitamin D. This was the case with the patient already mentioned whose plasma phosphatase was reduced after fourteen days of vitamin D therapy although at no time were there signs of rickets.

The rare occurrence of a normal phosphatase with signs of active rickets might be explained on the assumption that growth had temporarily ceased. As a result, even the negligible amount of minerals retained would suffice for the diminished activities of the bone cells.

Summary and conclusions

The plasma phosphatase was estimated in a group of 506 infants and children below the age of two years. In 84·1 per cent. of the cases with clinical or x-ray evidence of rickets the plasma phosphatase was increased above normal limits. It is suggested that a rise in plasma phosphatase is an earlier manifestation of the rachitic state than that provided by ordinary clinical or radiographic examination. A rough parallelism was observed between the height of the phosphatase and the severity of the rachitic process, but it is pointed out that the level of the phosphatase cannot be taken as an index of that severity in the individual patient. A moderate degree of correlation was observed between the rise in phosphatase and the fall in phosphorus and calcium phosphorus product, especially the latter, and it would appear that of the three, an increase in plasma phosphatase is the most delicate test of the rachitic state, although it would be unwise to use alteration in phosphatase alone as conclusive evidence of the presence or absence of rickets.

In untreated active rickets the plasma phosphatase continues to rise. Administration of vitamin D prevents this rise and in two to three weeks causes a fall. The rate of fall depends upon the dosage of vitamin D, being much more rapid with large amounts. On ordinary therapeutic doses normal limits may not be reached for over three months. The significance of a high plasma phosphatase is discussed, and it is suggested that the phosphatase is increased whenever the supply of calcium is unable to meet the demand of the bone cells as a result of defective intake of minerals or vitamin D.

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PERSISTENT TRUNCUS ARTERIOSUS COMMUNIS WITH MICROPHTHALMOS, ORBITAL CYST AND POLYDACTYLY

BY

H. A. HARRIS,
Anatomy School, Cambridge,

AND

G. C. THOMSON,
University of the Witwatersrand, Johannesburg.

Clinical record

A white woman, aged seventeen, was admitted to hospital in labour. Since the onset of menstruation at fifteen years only six or seven periods had occurred, and the last period could not be accurately dated. The personal and family history was uneventful. A female child was delivered by forceps after a lengthy first stage and cried spontaneously; she was apparently well nourished, was 50 cm. long and weighed 2,970 gm. (fig. 1). The lanugo was persistent and resembled that phase of distribution usually seen at the end of the eighth month. The orbits were sunken and the eyes were represented only by depressed slits 1 cm. in length with an interorbital distance of 3 cm. from one inner canthus to its fellow. Even with forcible retraction of the eyelids small eyeballs could barely be made out in the depths of the orbit. The ears were of the ' cauliflower ' type and presented marked Darwinian tubercles. The neck and trunk showed no abnormality and the umbilical cord was normal. An accessory thumb was present on the right hand and the skiagram showed two phalanges therein, the web between the two thumbs being slightly distal to the level of the interphalangeal joints. The genitalia were normal and there was a well-marked sacral dimple.

The child nursed poorly and the weight loss over the first four days was normal. During this period spells of rapid breathing and slight cyanosis were observed. The heart was found to be enlarged to the left and there was a loud systolic murmur best heard over the apical and pulmonic areas. The child became more cyanotic, the temperature rose to 101° F. and death occurred on the sixth day.

Post-mortem findings

The heart. The child was well nourished and there was marked livor mortis especially in the nails of the fingers and toes—a condition which is not infrequently associated with a congenital anomaly of the heart. The abdomen showed no abnormality except an incompletely descended caecum and appendix which were situated at the level of the right iliac crest. The lungs showed congestion and small areas of inflammation especially at the left base. The middle lobe of the right lung was not clearly demarcated from its neighbours and the interlobular fissures were shallow. The thymus was small and the pericardial sac globular in shape. The heart was enlarged especially on the right side and weighed 30 gm. It presented a single large artery at the base, a persistent truncus arteriosus, with no trace of the differentiation into pulmonary and aortic trunks. The truncus arteriosus

arose from the upper margin of the right ventricle, and was continued as a normally situated aortic arch with the three main arteries to the head and neck in the normal order. The recurrent laryngeal nerves were normally situated. Right and left pulmonary arteries arose from the posterior aspect of the truncus communis arteriosus at a distance of 9 mm. from its origin. The diameter of the right pulmonary artery was 4·5 mm. and that of the left 4 mm., the distance between the two at origin being about 2 mm. The ductus arteriosus, 8 mm. long and 1 mm. in diameter, ran from the left pulmonary artery to the convexity of the arch of the aorta and was patent

FIG. 1.—Post-mortem photograph of female babe, aged six days, with bilateral microphthalmos and polydactyly.

throughout. The pulmonary veins opened normally into the left auricle, the cavity of which was much smaller than normal and the auricular appendage was small and constricted at its union with the auricle. The superior and inferior venae cavae and the coronary sinus were normal, as were the Eustachian and Thebesian valves. The right atrium had a volume approximately five times that of the left atrium. The auricular septum was patent, and the foramen ovale measured 6 mm. from the thick border of the septum secundum below to the thin margin of the septum primum

above; antero-posteriorly on the sagittal plane the foramen measured 8 mm. As a result of the marked dilatation of the right auricle and its auricular appendage, the opening of the superior vena cava into the atrium appeared to be guarded by two thickened valves—the septum secundum to the left and the fold between the vena cava and expanded auricular appendage to the right.

The right ventricle occupied four-fifths of the anterior aspect of the heart and one-half of the posterior aspect. The right ventricular cavity was dilated and the muscular wall was 4 mm. thick, as compared with 5 mm. in the left ventricle. The ventricular septum was deficient, and its free

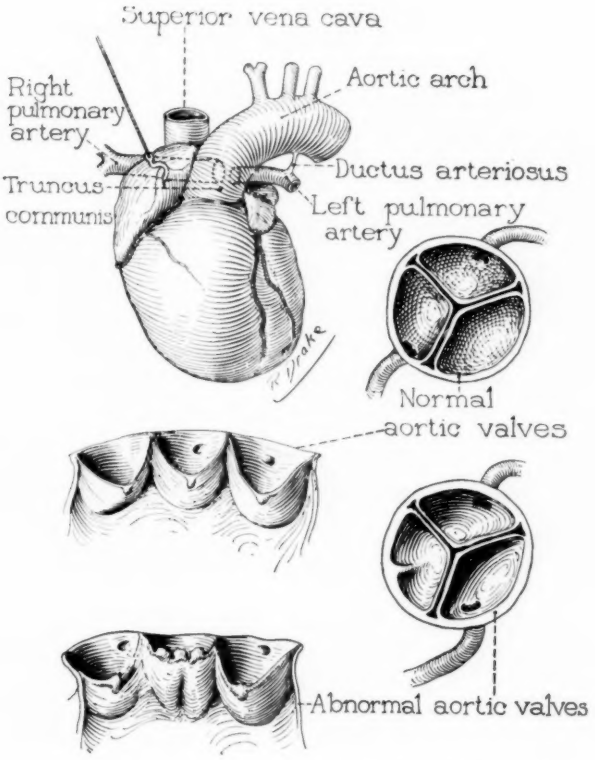

FIG. 2.—The heart of a female babe, aged 6 days, with truncus communis arteriosus from which the right and left pulmonary arteries arise. The abnormal aortic valves and coronary arteries are shown in comparison with the normal.

thickened margin directed backwards. On opening the truncus communis arteriosus by a continuation of the incision in the right ventricle, the free margin of the ventricular septum was concave and directed backwards and to the right so that the anterior proximal horn fused with the root of the truncus communis to the left anteriorly and the posterior distal horn fused with the truncus communis to the right posteriorly. The truncus communis was in more intimate relation to the dilated right ventricle than to the left, the free margin of the ventricular septum sitting so that the channel from the right ventricle to the truncus was about twice the area of that from the left.

The orifice of the truncus communis arteriosus measured 2·2 cm. in perimeter and presented two large valves and two small valves, the two latter measuring in total length the same as either of the former. The two small valves were not entirely separated from one another as the line of attachment to the aortic wall which separated them failed to reach the free margin of the valves (fig. 2). Each of the small valves contained a thickened

FIG. 3.—Section of the microphthalmic eyeball with cyst of the herniated retina. The pigmented layer of the retina lines the interior of the eyeball whereas the cellular layers of the retina are arranged around the vitreous and the hyaloid artery. Albuminous fluids occupies the intervening space.

nodule in the free margin thus suggesting that they should be regarded as separate entities, rather than as subdivisions of a single valve. All four valves were thickened and a considerable amount of fibrous tissue surrounded the corpus Arantii, so that the edges failed to meet closely. The right and left coronary arteries arose from the normal left anterior and the right posterior cusps; no accessory coronary arteries were found in relation to the two smaller cusps.

The mitral and tricuspid valves were normal and at the line of attachment the former measured 3·2 cm. and the latter 4·5 cm. in circumference respectively. No abnormalities were noted in the papillary muscles and chordae tendinae. There was no naked-eye sign of endocarditis.

The eyes. On separating the small palpebral fissures both eyeballs were found to be small and sunken. The diameter of the eyeballs was about 6 mm. The extrinsic muscles were all present, but small in size. The only abnormality was in the levator palpebrae superioris which was not as clearly separated from the superior rectus as usual. At the back of the eyeball was a small optic nerve of 0·5 mm. diameter. A mass of tissue occupied the retrobulbar space and this was removed with the eyeball for microscopic examination. The sclera over the posterior part of the eyeball was dense and opaque, but more anteriorly a certain amount of pigment

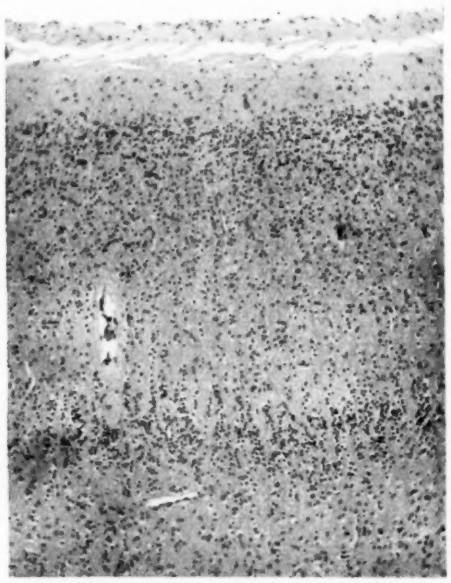

FIG. 4.—Microscopic section of the area striata of the visual cortex.

was visible through the thinner sclera. Details of the pupil and iris could not be made out as the anterior chamber of the eye was invaginated and the lens was dislocated downwards.

On histological section the eyeball showed extreme disorganisation. The retina was split between the basal pigment layer and the nerve cell layer proper so that the pigment layer lined the interior of the eyeball, and the cellular elements of the retina were thrown into folds surrounding a vitreous mass which contained a large hyaloid artery (fig. 3). An unorganized deposit of albuminous fluid lay between the retina and the pigment layer. Behind the eyeball was a cyst consisting of retinal elements surrounded by a fairly well-defined connective tissue. According to the view of Wolff[1] the cyst is formed as a result of the collection of albuminous fluid between the retina and the pigment layer. This fluid

causes the retina to be pushed out of the eyeball along the ocular fissure into the loose mesoderm. The evaginated portion of the retina forms a cyst which may grow to be larger than the eyeball itself. In this case the cellular elements of the retina in the cyst were not reversed, as is occasionally the case. It would appear that the retina was herniated at a time in embryonic life when the optic cup was incompletely invaginated and the chorioidal fissure was still incompletely closed at the pupillary margin. This stage of development, according to the views of Ida Mann[2], would be that of the fifth or sixth week of embryonic life.

The bony orbits were smaller than usual in their dimensions. On opening the skull the brain and cranial nerves appeared to be normal with the exception of the optic nerves and optic tracts. The optic nerves were only 0·5 mm. in diameter and the optic tract 0·7 mm. Scammon[3] states that the average diameter of the optic nerve in the newborn is 2·7 mm. On microscopic section both the optic nerve and optic tract displayed a considerable amount of aplasia, more marked in the former than the latter. The external geniculate body and the visual cortex, with a well developed stria of Gennari, were apparently normal (fig. 4).

The interest of these observations lies in the demonstration that a profound disorganization in one part of the visual mechanism, the eyeball and retina, involves to a decreasing degree the optic nerve and optic tract without causing any marked retrograde degeneration in the external geniculate body and the visual cortex. Had the babe lived for any considerable period of time, degeneration changes would probably have ensued in the visual cortex. Bolton[4] examined the area striata in a case of complete congenital anophthalmus and maintained that both the extent of the visual cortex and the cytoarchitectonic differentiation of the layers in relation to the stria of Gennari was impaired, so that the area of the former was reduced by one half. In this case the lamination of the area striata corresponds closely to the normal.

Embryological considerations

Maude Abbott[5] has collected thirteen cases of persistent truncus arteriosus in a series of 651 cases of congenital cardiac anomalies. The duration of life varied from one hour to twelve years. Defect of the auricular septum characterized six of the cases, and defect of the ventricular septum characterized all thirteen, as the pars membranacea septi is developed from the pulmono-aortic septum. Eight of the cases presented a right-sided aortic arch; the right ventricle was hypertrophied in ten cases and the left ventricle in seven. Marked cyanosis was reported in three cases and a loud second ' pulmonic ' sound in two. Six of the cases were complicated by defects in systems other than the vascular. Another case of persistent truncus arteriosus with defect of the auricular and ventricular septa was described by Harris[6].

The present case shows a total defect of the pulmono-aortic septum including the pars membranacea septi. The deficiency in the auricular septum is not great. The pulmono-aortic septum proper begins to develop

in the fifth week of embryonic life and the definite four-chambered heart is completely demarcated by the end of the seventh week. The interventricular septum commences to develop in the fourth week as a crescentic ridge on the inferior wall of the ventricle. The septum primum of the auricles begins to develop in the fifth week.

The associated anomalies in this case were bilateral microphthalmos, complete aplasia of the optic nerves and bilateral orbital cysts in direct communication with the interior of the eyeball. Is it possible to find a common time factor for the multiple anomalies? The condensation of the mesenchyme which is to form the dura mater sheath of the optic nerve is seen in a 10 mm. embryo, but actual axis cylinders of the optic nerve are not normally seen until the 20 mm. stage in the human. Again the anlage of the metacarpal of the thumb is clearly seen in the 16 mm. stage, a time when the precartilaginous differentiation of the phalanges is rapidly taking place. This suggests that the disturbance of development in the eye and in the thumb occurred between the 10 mm. and 16 mm. stage, which is approximately the fifth week. At this time the eye already has a definite lens and abundant retinal pigment, but the optic stalk is still open and is about to undergo closure. The failure of the regular closure together with the appearance of the albuminous exudate in the retina at this time leads to the orbital cyst which contains imperfectly differentiated elements of the retina and pigmented layer. The sum total of the cardiac, optic and skeletal anomalies occurring in the fifth week are obviously not incompatible with the continuation of embryonic life and none of the special processes of growth and differentiation occurring after this period seem to have been interfered with except in so far as they were essentially consequent upon the main lesions. It is noteworthy that the peripheral parts of the vascular system, the urogenital system and the lymphatic system display no anomalies as most of the critical processes therein antedate or postdate the aberrations associated with the fifth week of intra-uterine life.

Summary

1. A female infant of six days presents a truncus communis arteriosus, complete failure of the pulmono-aortic septum, deficient ventricular and auricular septa, microphthalmos, orbital cysts and polydactyly.

2. The site and nature of the anomalies point to an interference with normal growth during the fifth week of embryonic life, but the maternal history is negative.

Thanks are due to Dr. Otto Schwartz and Dr. Paddock of the Department of Obstetrics at the Washington University Medical School, who afforded the opportunity for examining the case, and provided the clinical history and photograph.

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CASE REPORT

ABNORMAL EXPANSION OF THE LUNGS IN AN INFANT

BY

BRANFORD MORGAN, M.D., M.R.C.P.
(From the Jenny Lind Hospital for Children, Norwich.)

Clinical record

A male infant, aged five weeks, was admitted to the Children's Hospital owing to the onset, soon after birth, of attacks of dyspnoea and cyanosis. He was a full term child; birth had been normal. Examination revealed the heart in the right thorax; the lungs were normal except for fine crepitations at both bases. X-ray pictures following a barium feed confirmed the position of the heart in the right side of the thorax, with no transposition of other organs. A diagnosis was made of dextroversion of the heart associated with further serious congenital abnormalities.

From the date of admission the attacks of dyspnoea accompanied by cyanosis gradually became more frequent, and death occurred fifteen days after admission, following continuous attacks of dyspnoea and cyanosis. Fourteen days after admission a systolic bruit was noted for the first time in the third right intercostal space, two inches from the mid-sternal line. During the last week there was a mild degree of pyrexia; the pulse rate throughout varied from 160 to 180, the respiratory rate from 40 to 76 per minute. The cyanotic attacks were to some extent relieved by inhalation of oxygen.

Autopsy

On opening the thorax the upper lobe of the left lung, much enlarged, was found lying transversely, posterior to the upper part of the sternum; a well-marked groove in this portion of the lung had been produced by the pressure of the sternum. The anterior portion of the lobe was dull white in colour and obviously emphysematous, whilst the posterior portion was dark and of normal texture. It was now clear that the displacement of the heart was the result of the abnormally situated left upper lobe (see fig. 1).

The specimen was shown to Dr. John Beattie, Conservator of the Museum of the Royal College of Surgeons of England, who kindly supplied the following report:—

Report on specimen of thoracic viscera of child H.

The specimen consists of the lungs, heart and great vessels of a child shortly after birth. The upper lobe of the left lung has expanded abnormally across the middle line and invaginated the right pleural sac, displacing the

thymus gland backwards and to the right. A well-marked groove on the anterior aspect of this lobe probably contained the sternum during life, and suggests that considerable pressure had been exerted on the great vessels. The upper lobe of the right lung had not expanded, and only partial expansion of the lower lobe on this side had taken place. The lower lobe of the left side was normal. Examination of the specimen revealed no embryological defect, but it was observed that the upper branch of the left pulmonary artery had been acutely kinked around the ductus arteriosus.

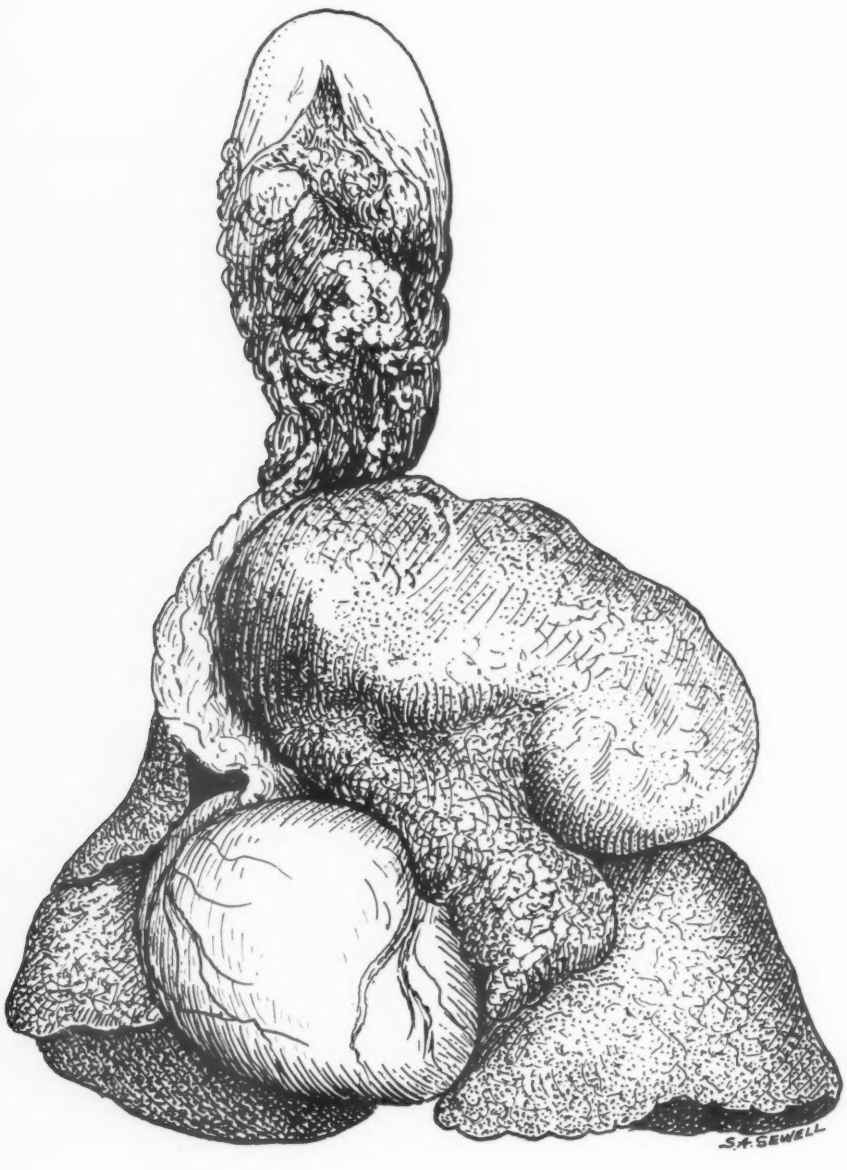

FIG. 1.—Line drawing showing transverse position of upper lobe of the left lung and displaced heart.

The abnormality seems to be best explained by a deficient expansion of the right lung, followed by a compensatory emphysema of the left lung. The kinking of the pulmonary artery and the trapping of the left upper lobe behind the sternum, may have contributed to some extent to the persistence of the emphysematous condition. The cause of death can only be guessed at, but it seems probable to me that interference with the great vessels due to pressure may have contributed if it was not the only cause of death. A histological section of the emphysematous lung demonstrates quite clearly that there was no inflammatory reaction within the lung itself.

Comment

From the clinical aspect the interest of the case centres on the diagnosis from congenital dextrocardia, of that type in which the heart is simply rotated and lies in the right side of the chest; is unassociated with the transposition of the cardiac chambers; and is almost invariably associated with some serious congenital anomaly. Such a diagnosis gave a satisfying explanation for the paroxysms of cyanosis and dyspnoea. The autopsy, however, revealed what so far as can be ascertained from a search of the literature is a hitherto unrecorded cause of extrinsic dextrocardia, and as such the case is published.

Etiologically the condition might be explained by atelectasis of the upper lobe of the right lung, followed by compensatory emphysema of the upper lobe of the left lung, and the occupation by the latter of space normally occupied by the former. Alternatively, it is recognized that expansion of the lungs in the newborn is a gradual process, taking place unequally throughout the lungs and requiring two to three days or longer for full inflation, and it seems feasible that expansion of the upper lobe of the right lung might be delayed to such an extent as to lead to compensatory emphysema of the corresponding lobe on the opposite side. The systolic bruit which developed during the course of the illness was no doubt the result of distortion of the great vessels, as described in Dr. Beattie's report.

FAMILIAL PROGRESSIVE DIFFUSE CEREBRAL SCLEROSIS OF INFANTS

BY

DOROTHY S. RUSSELL, M.D.,*

AND

KENNETH H. TALLERMAN, M.D., F.R.C.P.

The published accounts of progressive familial sclerosis of the brain in infants differ sufficiently in their histopathological details to warrant the description of additional cases of this rare condition, especially when such cases supply connecting links between those already recorded. By such a linking up it will doubtless become possible to recognize and relate phases in a single morbid process and perhaps to simplify the formidable nomenclature that has resulted from the claims of various authors to distinctive types.

In the following examples two infants, a brother and sister, suffered from a cerebral disease which was apparently familial and progressive in nature. Unfortunately the brain of the second child only was available for pathological examination. This example shows a combination of features that renders it different from, although evidently closely related to, certain others already recorded in the literature. After the death of this second child in 1932 a third was born in May, 1933. It has remained in good health up to the time of writing and now, at the age of three-and-a-half years, is normal in every respect. A fourth child, a normal female infant was born in October, 1936 and at the age of four months she was reported to be progressing normally.

Case records

Case 1. D. D. Male infant, aged 5 weeks.

FAMILY HISTORY. The parents are Jewish and first cousins. There was no history of disease in the family. This was the first child, and there had been no miscarriages.

HISTORY OF PATIENT. The infant was a full-term child, weighing 7½ lb. at birth, after a normal labour. He was fed at the breast, with supplementary feeds of a condensed milk mixture. He was quite well until the age of two weeks when he had a fit of crying, lasting four hours. On the

* Working for the Medical Research Council at the Bernhard Baron Institute of Pathology, the London Hospital.

following day he appeared well, but was unable to suck properly. Fifteen days before admission to hospital he still was unable to suck, and was fed by spoon. At this time he had a convulsion, and some head retraction was noted; the mouth was kept open. Owing to the fact that he was taking food and fluid badly, and was dehydrated, a diagnosis of ' dehydration fever ' was made. Subsequently further convulsions occurred, and three days before admission to hospital he was noted to be sleepy; he was hardly able to swallow, and fluids ran out of his mouth.

On December 19, 1929, he was admitted in a comatose condition to the Children's Department of the London Hospital, under the care of Dr. A. G. Maitland-Jones, by whose courtesy the case is reported. The temperature was then 97° F. The lungs, heart, and abdomen were normal. The legs were spastic; the knee jerks were equal and exaggerated; the optic discs were normal. On 20.12.29 some twitching of the face was noted. There was great difficulty in swallowing. The cerebro-spinal fluid was under pressure, and was blood-stained, but this was probably due to trauma from the needle. There was no excess of white cells, the protein content was 0·8 per cent. and the Wassermann reaction was negative. On 22.12.29 death occurred, just before which the temperature rose to 100·8° F. No post-mortem examination was obtained. A diagnosis of cerebral haemorrhage was made. In the light of subsequent events, however, this seems to be incorrect, and it appears justifiable to regard the condition as one of familial progressive diffuse cerebral sclerosis.

Case 2. C. D. Female infant, aged 6 months.

FAMILY HISTORY. The one previous child died as a result of cerebral disease, as described above. No other history of illness.

HISTORY OF PATIENT. The infant was born at full term, weighing $7\frac{1}{4}$ lb., and the labour was normal. At birth the child was apparently healthy in every way, and she remained so for the first three to four months, except that she was never hungry, and would take about an hour on an average over each feed, sucking spasmodically. She would become less and less inclined to feed as the day progressed, so that by the time the last feed was due, at 10 p.m., she could seldom be induced to take anything. In spite of this she put on weight steadily, about 4 to 5 oz. weekly, was a moderately active child, with a normal cry, and slept well. At five weeks of age she refused absolutely to take a breast feed, and was put on a dried milk mixture. There was slight vomiting from time to time, but this was never serious, and later ceased. At three-and-a-half months of age she developed what was described as a ' bad cold in the eyes.' Both eyes were closed by a swelling of the lids which lasted four or five days, and then gradually subsided; there was no accompanying nasal catarrh or cough. At about four months of age she became less active, and appeared to be growing weaker, the arms and legs being slightly stiff. Her healthy cry now changed into a prolonged whimper, and she gradually failed to show any definite recognition of any person or thing. About this time twitching was noticed in the left side of the face, the left arm, and the left leg, but this passed off. At five months she began to cry whenever she was handled. On account of this and her other abnormalities she was seen in consultation by one of us (K. H. T.). There was no history of attacks of cyanosis, and no fever had been noted. The bowels moved normally.

ON EXAMINATION. 29.11.31. The infant weighed 14 lb. 5 oz. There were no definite neurological signs: no head retraction, nor apparent cervical rigidity; no bulging of the anterior fontanelle; no signs of deafness. The

limbs appeared to be moved normally. The knee jerks were equal and normal. The pupils reacted to light, and no abnormality was noted in the fundi, but they were difficult to examine. The eyelids were puffy, and the eyes had a staring appearance. The heart was not enlarged, but there was a systolic murmur, unaccompanied by thrill and localized to the second and third left inter-costal spaces close to the sternum.

It was considered at this time that the child might be suffering from some form of cerebral degeneration, but there was no definite evidence of this, and the acute symptoms appeared to be due to feeding irregularities, which might be held responsible for colic and difficulty in taking the feeds. These irregularities were corrected and the diet adjusted, but the child failed to progress, and after about three weeks developed gastro-enteritis with blood-stained motions, and at the same time definite spasticity of the limbs and general rigidity. On this account she was admitted to Paddington Green Children's Hospital.

On admission. 22.12.31. Clinical examination revealed a well-nourished infant, weighing 12 lb. 8 oz., who remained lying on her side, with eyes usually closed (there being now no oedema of the lids), head slightly retracted, arms flexed with fingers tightly clenched, and legs and feet stiffly extended. She showed no signs of visual recognition, nor of auditory sensation. She did, however, show by whining a resentment at being moved. The anterior fontanelle was open, and neither depressed nor bulging. The ear drums were normal. The left optic disc was rather pale; there were no changes in the vessels, no papilloedema, and no abnormality of the macula. The right fundus appeared normal. There was slight rigidity of the neck muscles, and marked rigidity of the arms and legs, the arms being in semi-flexion with the fists tightly clenched, and the legs in extension. The knee jerks were slightly increased; owing to rigidity there was difficulty in eliciting ankle and triceps jerks. The plantar response was extensor on both sides, and the abdominal reflexes were absent. The heart showed the same signs as on the previous examination. There was no clubbing of the fingers, no cyanosis, and no dilatation of veins.

Lumbar puncture produced a clear fluid under slightly increased pressure, showing no abnormality: the Wassermann reaction was negative, and the urea content 18 mgm. per 100 c.c.

A specimen of urine obtained by catheter was normal. There was a slight vaginal discharge, and in a non-catheter specimen some pus cells were noted.

Progress. 29.12.31. The child was still sucking extremely badly, and would hardly take feeds at all, the milk having to be poured from the bottle into her mouth. There was no vomiting, and the motions were normal. She was more lethargic than ever, and remained motionless, with eyes closed, head slightly retracted, arms semi-flexed, and legs extended. She was, however, gaining weight satisfactorily.

The fundi were examined by Mr. Frank Law, who reported that vision appeared defective, but it was difficult to form an accurate opinion regarding this, in view of the child's condition. Both discs appeared to be within the limits of normality, and there was no papilloedema. There were no mascular lesions to be observed, and the vessels were normal. The child did not follow a light with her eyes, but there was a slight sluggish contraction of the pupils to light. There was no reaction to any loud noise.

31.12.31. There was now great difficulty in swallowing, and almost continuous dribbling from the mouth; the child had to be fed by tube.

2.1.32.* The attitude now suggested complete decerebrate rigidity (fig. 1). Both pupils showed a very sluggish and slow reaction to light, and a consensual reaction—the right rather stronger than the left. There was a doubtful grasp reflex of the hands, but none of the feet. The tone of the arms, in both extension and flexion, was influenced by the position

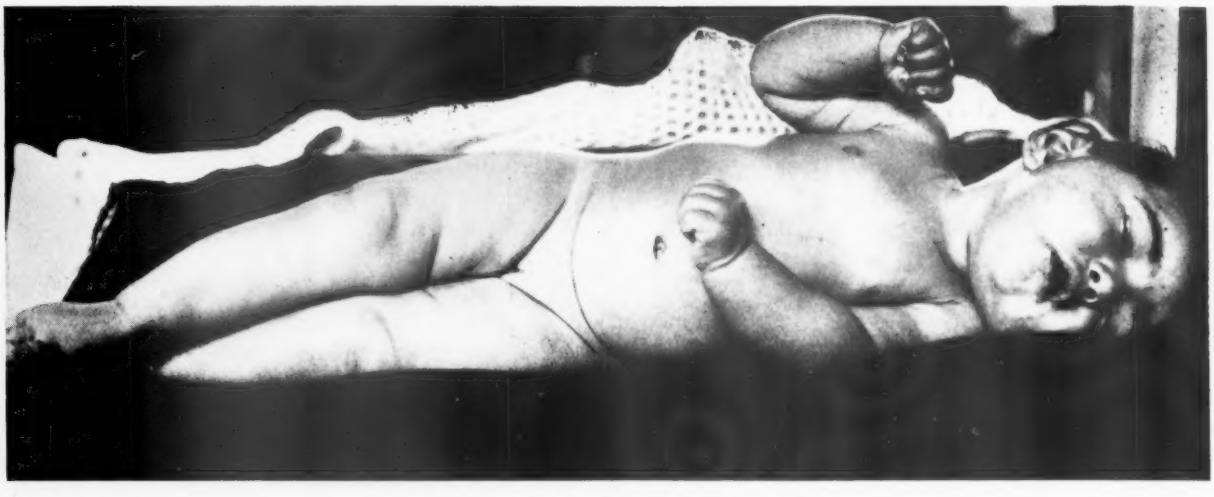

FIG. 1.—C. D., 2 days before death.

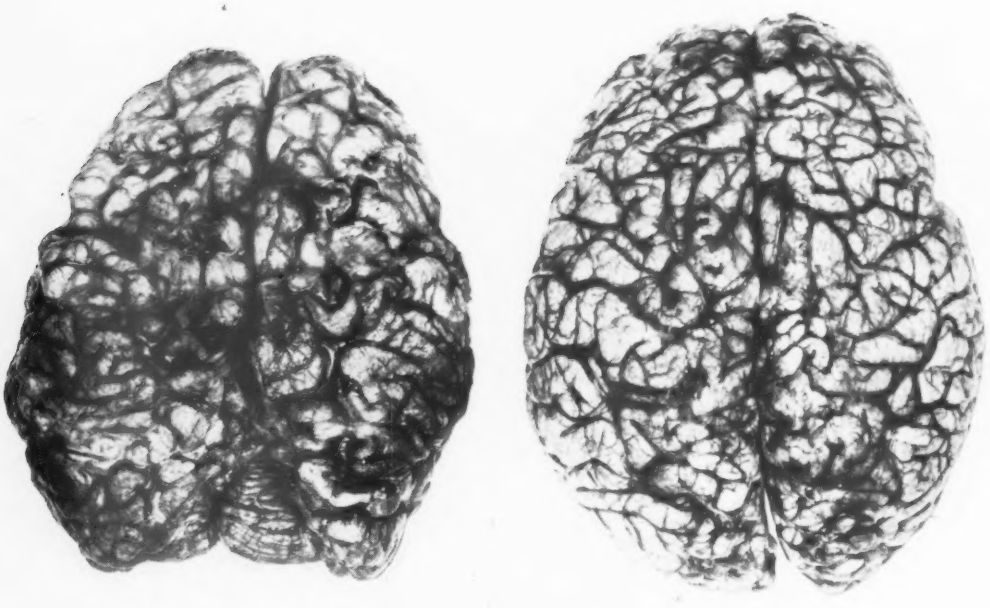

FIG. 2.—Dorsal view of brain after fixation; on right, control of same age.

of the head: when the head was turned to the left or to the right, the extension tone of the left or the right arm respectively was increased. Both extension and flexion reflexes could be elicited in each arm, depending upon the position of the head. Similar tone responses in the legs could be elicited.

* Patient seen in consultation with Dr. W. R. Brain.

5.1.32. Weight, 12 lb. 10 oz. Mr. F. Law now reported that the left optic disc was pathologically pale, and the right disc appeared to be becoming so.

Diagnosis was made of progressive familial cerebral degeneration, and congenital morbus cordis.

6.1.32 The child was unable to swallow.

7.1.32. Death occurred at 3 a.m. There was no terminal fever, and throughout her stay in hospital the child had been afebrile.

Pathological examination*

NECROPSY. Permission for examination was restricted to the head. The brain when exposed appeared abnormally small and somewhat congested. The cerebral convolutions were narrow and worm-like and were separated by abnormally wide sulci (fig. 2). The subarachnoid spaces contained an excess of cerebrospinal fluid, the leptomeninges being normal except for slight opacity over the circle of Willis. The cerebral atrophy was most conspicuous in the fronto-parietal region and was not appreciable either in the temporal lobes or on the ventral aspect of the hemispheres.

After fixation in formaldehyde the brain weighed 14 oz. (397 gm.) representing approximately a fourteenth part of the total body weight. The brain of a control male infant of the same age weighed 25 oz. (709 gm.), a sixth part of the total body weight. Comparison with the control also showed a considerable flattening of the hemispheres and atrophy of the lateral cerebellar lobes. The brain as a whole felt abnormally soft but on section the texture varied greatly in different areas. The white matter was soft throughout the greater part of the hemispheres, and appeared friable and greyish-yellow beneath most parts of the cortex. Demarcation of the cortex and white matter was blurred. The white matter of the convolutions was extraordinarily spongy, containing small irregular spaces measuring up to 3 mm. in diameter. Such convolutions appeared greatly wasted, but the basal parts more so than the tips so that, on the cut surfaces, the convolutions were often club-shaped (fig. 3). A similar spongy change was present in the external capsule and island of Reil. Numerous sharply defined cystic areas (up to 0·4 × 0·2 cm.) were scattered throughout the basal ganglia with the exception of the caudate nuclei (fig. 5). They were mostly grouped about the internal capsule, occupying both the lateral border of the optic thalamus and the globus pallidus. In the parieto-occipital region, in the putamen, and in scattered ill-defined areas beneath the cortex of all lobes the brain was ivory-white and its texture was very tough and rubbery. This alteration caused considerable obscuration of the pattern in the posterior parts of the basal ganglia.

Foci of greyish-white softening were present in the tegmental part of the mid-brain; the rest of the brain stem appeared normal. The changes in the cerebellum resembled those in the cerebrum. The folia were narrow and atrophied (fig. 7). An opaque creamy-yellow line separated the cortex from the white matter and the latter was for the most part spongy with a slight greyish discoloration. The central parts of the lateral lobes were rather firm and rubbery.

A relative degree of internal hydrocephalus was present, affecting chiefly the posterior horns of the lateral ventricles. The ependyma everywhere was smooth and glistening and the choroid plexuses appeared normal.

MICROSCOPIC EXAMINATION. The leptomeninges appear normal except for the presence of occasional groups of lymphocytes and plasma cells near the blood vessels upon the convexities. There is no infiltration of the basal leptomeninges.

* London Hospital records—P.M. 586, 1930, Appendix.

FIG. 3.—Frontal cortex showing atrophy, especially of bases of convolutions, and gross loss of myelin. Loyez haematoxylin. × 3·3.

FIG. 4.—Control for fig. 3. Corresponding part of frontal cortex showing myelination. Loyez haematoxylin. × 3·3.

FIG. 5.—Coronal section of basal ganglia showing atrophy, cystic areas and loss of myelin. Loyez haematoxylin. × 3.

FIG. 6.—Control for fig. 5, showing normal pattern and myelination in infant of same age. Loyez haematoxylin. × 3.

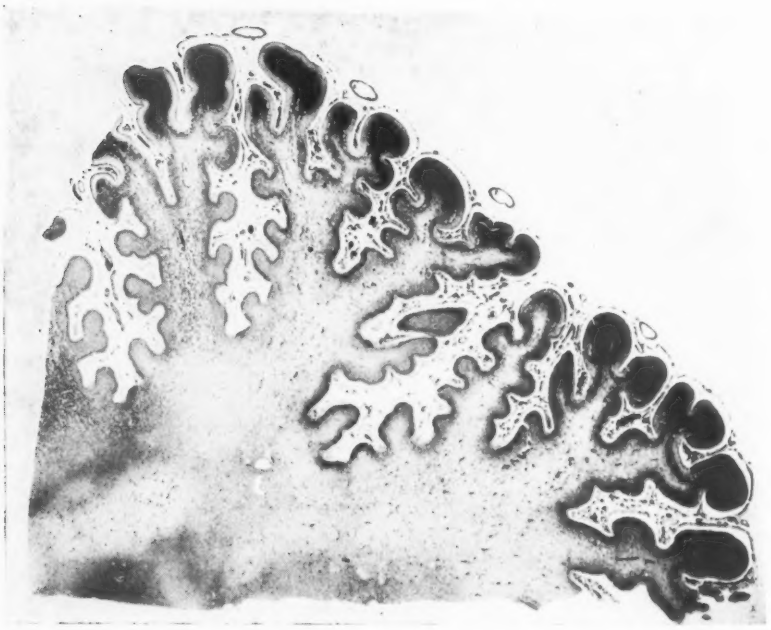

FIG. 7.—Cerebellum showing atrophy of folia and great loss of myelin, except at summits of folia. Loyez haematoxylin. × 4.

FIG. 8.—Control of same age showing normal contours and myelination. Loyez haematoxylin. × 4.

In the cerebrum degenerative changes are in general pronounced. In the hippocampus alone the normal structure is preserved and the myelinated fibres are here intact. In the convolutions of the adjacent temporal lobe there is a gradual transition to the changes that prevail in all other parts of the cerebral convexities that were examined. In these there is great destruction of the cortex except at the summits of the convolutions (fig. 3). Here the pyramidal cells are recognizable and are of nomal size and shape but their nuclei appear vesicular and the Nissl bodies are scanty and are confined to the periphery of the cell. No lipoid inclusions are present in Herxheimer and Marchi preparations. In the depths of the sulci there is often a complete absence of bodies of neurones and decreasing stages of degeneration can be traced as the summits are approached. Myelin sheaths cannot be recognized in the cortex. In Bielschowsky preparations both tangential and radial axis cylinders are present at the summits of the convolutions and they appear well preserved; in the cortex in the depths of the sulci a few tangential axis cylinders only are recognizable. Associated with this destruction of neurones and proportional to it is a conspicuous infiltration of the cortex with amoeboid forms of microglia containing lipoid material giving a positive reaction with the Herxheimer and Marchi methods. These cells sometimes lie in an irregular, ill-defined zone beneath the pia and form discrete foci in deeper parts of the cortex. Numerous astrocytes are also present in the depths of the sulci (fig. 11). They are often fibrillated and have relatively large cell bodies with clear, glassy cytoplasm. In places the cortex is entirely replaced by diffuse patches of dense fibrillary gliosis. There is no infiltration with cells of the types that characterize known infections. The adjacent white matter is often honeycombed with small irregular spaces, especially in the convolutions. Such areas show extremely few axis cylinders in Bielschowsky preparations and their course is disturbed by the presence of the spaces. Loyez and Weigert Pal preparations show conspicuous degrees of demyelination when compared with a normal control of the same age (fig. 3 and 4). The naked-eye appearance of Weigert-Pal preparations of a coronal section through the whole hemisphere in the parieto-occipital region corresponds approximately, in the degree of myelination, to Flechsig's demonstration[3] in a child of four months. The optic radiations are well preserved. With high magnification extensive destruction of the myelin is demonstrated by ballooning of the sheaths and by wide dissemination of globular fragments of myelin of various sizes. The deficiency of myelin is in general diffuse throughout the centrum ovale and does not appear excessive in perivascular areas. Associated with this loss of myelin and proportional to it is an overgrowth of fibrillary astrocytes. These astrocytes, like those present in the cortex, have a somewhat swollen cytoplasm and in Herxheimer and Marchi preparations frequently contain small granules of fatty substances. The Marchi preparations do not show droplets of fat outside the cells. No infiltration with cells of the types that characterize known infections is present, and the blood vessels are unaltered except for occasional cuffs of lipoid-containing cells in the adventitial sheaths. The oligodendroglial cells are not noticeably reduced in number. Those present in areas of degeneration and gliosis show advanced degrees of ' acute swelling,' often reaching the stage where the nucleus is very pyknotic and the cytoplasm is disintegrating.

The changes in the cerebellum resemble those noted in the cerebral hemispheres. The cortex shows great destruction with replacement of its normal elements by numerous astrocytes and amoeboid microglial cells containing lipoid, except at the summits of the folia where the superficial embryonic granular layer, inner granular and Purkinje cells are demonstrable (fig. 7). The Purkinje cells show stages of degeneration, which

become more intense as the depths of the sulci are approached. Here these cells are usually absent and the granular cells are greatly reduced in numbers. The white matter shows extreme demyelination and porosity. In Bielschowsky preparations the axis cylinders are greatly reduced in numbers; those present are well preserved but are displaced by the numerous pores. These degenerative changes are accompanied by great gliosis, especially near the centres of the lateral lobes. There are only a few fat-granule cells in these central parts but they become ever more abundant as the cortex is approached. The astrocytes on the other hand often contain granules of fatty material. There is a considerable reduction in the numbers of oligodendroglial cells throughout the white matter.

In the basal ganglia the cystic areas observed with the naked eye are crossed in places by vascularized trabeculae of neuroglia coated with

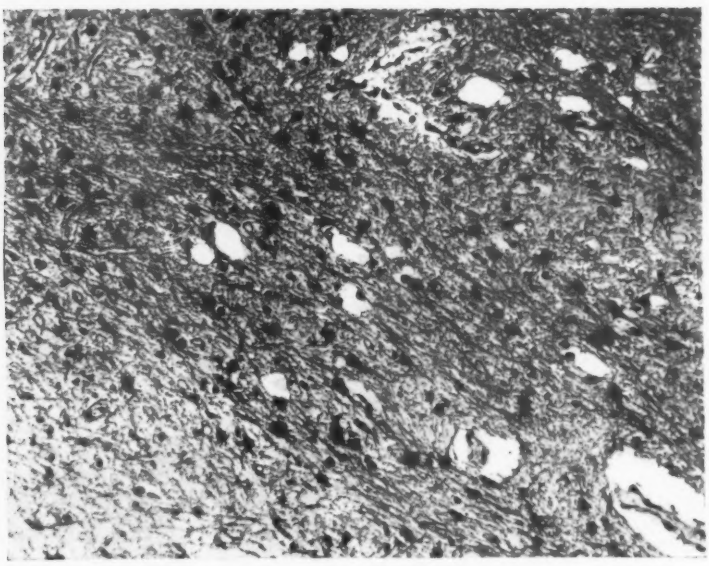

FIG. 9.—Lenticular nucleus showing dense fibrillary gliosis. Mallory's phosphotungstic acid haematoxylin. × 159.

amoeboid microglial cells containing lipoid droplets. A few of these cells lie in the cavities, which are otherwise empty. In one of the trabeculae a vessel shows endarteritis fibrosa and perivascular infiltration with lymphocytes and a few plasma cells. No endarteritis was found elsewhere and perivascular infiltration of the same character was found only in two vessels attached to the right ventricular choroid plexus and in one perforating vessel in the pons. In Herxheimer preparations there are cuffs of fat granule cells in the perivascular sheaths of many vessels and a few amoeboid microglial forms containing fat are diffusely distributed beneath the ependyma covering the optic thalami. The ependyma is intact. There is gliosis with loss of bodies of neurones in the globus pallidus becoming more intense in the putamen, which is occupied by a gliosis which is so dense and cellular that it resembles an astrocytoma (fig. 9, 10). The optic thalamus and caudate nucleus are less affected, the degeneration of bodies of neurones and gliosis

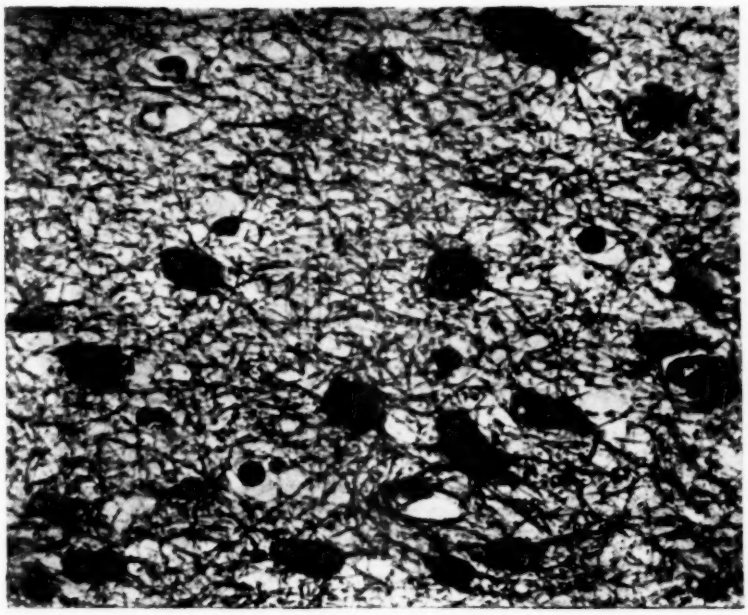

FIG. 10.—Same as fig. 9 to show astrocytes and fibrils. × 600.

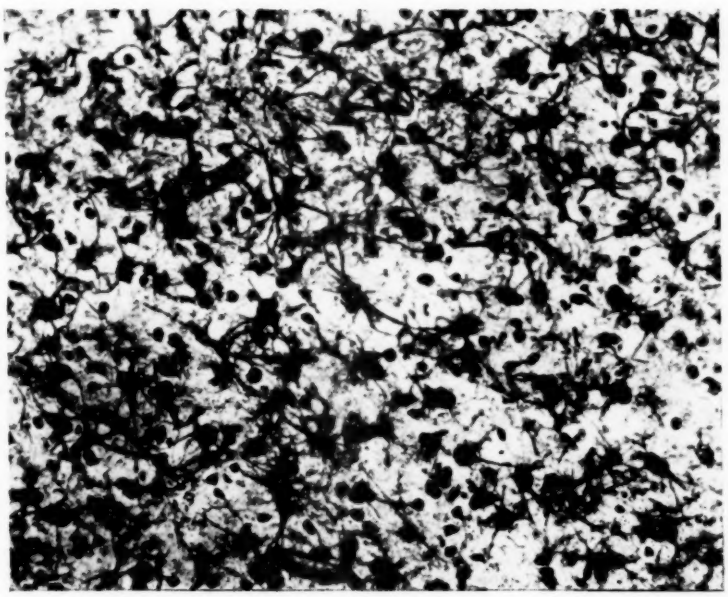

FIG. 11.—Occipital cortex in depths of a sulcus showing excess of fibrillary astrocytes. Hortega's silver carbonate (Penfield's modification). × 190.

being less conspicuous. The lateral parts of the thalamus, adjacent to the internal capsule, are more affected than the medial and show, in Hortega preparations, an excess of microglial cells. There is great fragmentation of myelin in the internal capsule and here, as elsewhere, the process is diffuse. Bielschowsky preparations show great loss of axis cylinders in areas of degeneration. In the internal capsule they are surprisingly well preserved and appear fairly numerous. The hypothalamus appears normal and the optic tracts are well myelinated.

In the mid-brain degeneration is limited to a few symmetrical areas in the tegmental region. The largest of these occupies the medial fillet, arching round and encroaching on the dorso-lateral aspect of the red nucleus. Other smaller areas lie on either side of the aqueduct. Gliosis and fragmentation of myelin are visible in these areas and, in frozen sections, fat-containing microglial cells are present. The oculo-motor nuclei appear porous and contain a few collections of fat-granule cells. The bodies of neurones however are well preserved. Gliosis is most marked in the red nuclei and is also conspicuous throughout the tegmental region, continuing with decreasing intensity caudalwards to fade away in the upper medulla. The oligodendroglial cells do not appear to be reduced in numbers; they have undergone only slight degrees of acute swelling except in the areas of degeneration mentioned. The cranial nerve nuclei appear well preserved.

Summary of pathological examination

The pathological process appears to be a widespread degeneration affecting principally the cerebral and cerebellar white matter, but also involving the cortex in both situations. Degeneration is demonstrated macroscopically by atrophy of the brain attended by softening and porosity of its substance and microscopically by evidence of demyelination accompanied by a marked microglial reaction and an uneven gliosis. The oldest lesions appear to occupy the white matter of the parieto-occipital regions, putamen and the central parts of the lateral cerebellar lobes; foci of approximately equal age are scattered throughout the remaining parts of the cerebral hemispheres. The cerebral and cerebellar convolutions appear in general to have been more recently affected. A remarkable feature is the constant involvement of the cortex in the depths of the sulci and its relatively good preservation at the summits of the convolutions. Apart from the hippocampal convolutions, the hypothalamus and optic tracts, which appear unaltered, the degeneration is remarkably diffuse and there is no evidence of an initial perivascular distribution. The extreme degeneration of the oligodendroglial cells accords with other evidence of degeneration. It is well known that these cells are particularly vulnerable; their sensitivity is manifested by a series of changes known as ' acute swelling ' (Penfield and Cone[12]), the early stages of which can be detected within a few hours of death. In these circumstances it is not believed that the cerebral changes as a whole are attributable to an initial attack upon the oligodendroglia, as has been suggested by Hortega in connection with Schilder's disease and by Greenfield[5] in his description of two cases of progressive cerebral sclerosis in infants.

Evidence of inflammation of the kind that characterizes known infections is limited to scanty focal meningeal and perivascular infiltration with lymphocytes and plasma cells; in one vessel there is endarteritis fibrosa. There is no evidence of vascular proliferation in any part of the brain

examined. The cerebellum shows the same widespread destructive changes as the cerebrum. Apart from foci in the tegmental region the brain stem and cranial nerve nuclei are unaffected. The spinal cord was not available for examination.

Discussion

Estimation of the intensity of the demyelination is rendered exceedingly difficult by the age of the child, the onset of the disease having taken place at a time when the brain is normally undergoing rapid myelination. The fact that the disease in this instance began at about the age of four months and that Weigert-Pal preparations of some parts of the brain corresponded approximately with Flechsig's demonstration in an infant of four months might suggest that the appearances seen are due to an inhibition, or alternatively an aplasia, of normal myelination rather than to an active destruction of formed myelin. This view is unacceptable because it offers no explanation of the porous areas and small cysts in the white matter and basal ganglia, nor is it likely that a purely passive inhibition would be attended by the conspicous microglial reaction seen in this case. Moreover in areas, such as the Rolandic, where myelination is normally completed at an earlier age there is evidence of a conspicuous loss. An active degeneration is also indicated by the widespread involvement of the cortex resulting in the loss of bodies of neurones and a replacement gliosis (fig. 11). It is, however, reasonable to assume that, in the presence of a degenerative process of this character, the normal process of myelination would be in abeyance.

The remarkable absence both of infiltration with cells of the types that characterize known infections and of vascular proliferation further identifies the pathological process as a degeneration. There is no evidence from either a clinical or pathological standpoint of the nature of the damaging agent. The swollen bodies of the astrocytes in areas of gliosis (fig. 10) resembling the so-called ' gemästete ' glia cells and the extreme degrees of acute swelling of the oligodendroglia are suggestive of the action of a toxin.

Diagnosis. Although the familial incidence, Jewish parentage and clinical picture are suggestive of family amaurotic idiocy this diagnosis is ruled out by the absence of the characteristic macular changes and by the histological appearances of the brain. In particular there was no storage of lipoids in the neurones.

Familial examples of diffuse cerebral sclerosis have been described in young children, notably the familial infantile form of ' diffuse brain

sclerosis ' of Krabbe[7], ' aplasia axialis extracorticalis congenita ' or Pelizaeus-Merzbacher's disease (Pelizaeus[11]; Merzbacher[8]), and the ' progressive subcortical encephalopathy ' of Globus and Strauss[4]. Case 2 resembles Krabbe's cases clinically not only in the onset in early childhood and the rapid progression of the disease, but in respect of the presumptive familial tendency. Pathologically there is in both a conspicuous gliosis and demyelination of both cerebrum and cerebellum. The perivascular sheaths are infiltrated with fat-granule cells and there is remarkably little infiltration with cells of the types that characterize known infections. The present case, however, differs in the marked involvement of the cortex in both cerebrum and cerebellum, the occurrence of porous areas in the white matter accompanied by great irregularity in the glial proliferation, and the presence of numerous fat-granule cells in the brain parenchyma. These inconsistencies however are probably not indicative of any fundamental difference in the nature of the process, but may be interpreted as evidence of a more rapid destruction of the brain tissue in the present case with death at a time when scavenging and gliosis were incomplete. This interpretation finds some support in the description by Globus and Strauss[4] of four cases of Krabbe's type. In their third case in a female infant of six-and-a-half months, clinical deterioration was rapid, death occurring four days after the apparent onset of the illness. The brain in this case showed a diffuse but less uniform destruction of myelin than in their more chronic cases, associated with a ' status spongiosus ' of the subcortical tissue. ' Transitional forms leading to the formation of compound granular corpuscles were also found.'

The present case is distinguished from Pelizaeus-Merzbacher's disease again by the involvement of the cortex but more particularly by the conspicuous gliosis in both cortex and white matter, which has not been demonstrated in this form. While the clinical and histological features of the present case are strongly suggestive of Schilder's disease the involvement of cortex again might be considered to weigh heavily against this diagnosis, as does the apparent familial incidence. Bouman[1] has, however, pointed out (p. 120-121) that some degree of cortical change has been recorded by numerous observers in Schilder's disease. Of special interest, in comparison with the present case, is the description by Neubürger[10] of degeneration of the deepest layer of the cortex in the neighbourhood of the arcuate fibres. Bouman also finds (p. 104) that familial instances of diffuse sclerosis are now being reported with greater frequency. This statement has recently been repeated by Meyer and Tennent[9] in their paper on a fresh instance of familial Schilder's disease. The resemblance between these familial cases in infants and Schilder's disease is indeed emphasized by Globus and Strauss who regard both as a degenerative condition of toxic origin and suggest

that they should be grouped under the general name of ' progressive degenerative subcortical encephalopathy.' The inter-relationships of these groups and their possible kinship with disseminated sclerosis has been discussed by Bouman, who gives a comprehensive review of the literature.

Etiology. It is generally agreed that the etiology of all these forms of diffuse sclerosis is quite obscure. The possibility that viruses are responsible for the so-called demyelinating diseases of the central nervous system has been entertained for some years by competent authorities. In this connection the recent investigation by Innes[6] into a disease of lambs, ' swayback,' which resembles Schilder's disease in man, is of the greatest interest and importance. He states that ' all attempts to incriminate either bacteria or a virus have failed, and it appears improbable that these play any part in the etiology.' The causal agent, whatever it is, exerts its action while the lambs are in utero and does not appear to affect the health of the pregnant ewes. Innes discusses the possibility that lead may play some part and points out that punctate basophilia was found in many of the lambs with ' swayback.' In this connection it is of interest that Cone, Russel and Harwood[2] have independently found evidence suggesting that lead may be responsible for disseminated sclerosis. On the other hand, Rivers and Schwentker[13] have succeeded in producing an experimental encephalomyelitis accompanied by myelin destruction in a series of monkeys by injections of heterologous brain material. They were unable to demonstrate any infective agent to which the lesions might be attributed. Another theory attributes cerebral sclerosis in infants to an aplasia of myelin. This may be more readily applied to cases of the Pelizaeus-Merzbacher type in which the cortex is unaffected and there is no histological evidence of active myelin destruction. But on this basis it might be expected that symptoms would be apparent from the time of birth, which in general is not observed. In the present case the theory is unacceptable for reasons that have already been given.

In view of our ignorance of the etiology it is considered that nothing is to be gained by elaborating the classification of these cases. The present example is regarded as essentially of the same type as those described by Krabbe, by Globus and Strauss and by Greenfield. It is suggested that the term ' familial progressive diffuse cerebral sclerosis ' is sufficiently descriptive of the condition.

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PLASMA PHOSPHATASE AND PHOSPHORUS DURING THE HEALING OF FRACTURES IN CHILDREN

BY

OLIVE D. PEDEN, B.Sc.

(From the Surgical Department and Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

Robison and his co-workers[7] have shown that phosphatase is closely associated with the process of calcium deposition in bone. Wilkins and Regen[9] and Botterel and King[2] found that in animals there was an increase in the phosphatase activity of bone at the site of fracture: this began about four days after the injury and reached its maximum about seventeen days later. It is to be expected therefore that the plasma phosphatase which is derived at least in part from bone, would show changes during the process of repair following an injury to bone. Kay[5] and Bodansky and Jaffe[1] found that there was an increase in plasma phosphatase at this period. Hunsberger and Ferguson[3] in eighteen patients observed an increase occurring some time after the fracture and a slow reduction as healing took place. In a recent paper Mitchell[6] gave the results of serial determinations in seventy-five adult patients with fractures. He found that in many cases there occurred a slight increase in plasma phosphatase which was not proportional either to the amount or rate of healing.

The present investigation was undertaken in order to determine if in children in whom the bone-forming mechanism is much more active than in adults, a greater rise in the plasma phosphatase after an injury to bone could be demonstrated. The ages of the patients ranged from five to twelve years. Plasma phosphatase, serum inorganic phosphorus and calcium were determined in sixty-two patients. In thirty-seven cases this was done within three days of the fracture, in twenty, six to eight days later, in twelve on the thirteenth to the fifteenth day, in four on the twenty-second day and in ten on the fourth week or later. Unfortunately it was not considered advisable to repeat a blood analysis in more than a few patients.

The method adopted for the estimation of phosphatase was that of Jenner and Kay[4]. By this method it has been found[10] that in apparently healthy children of three to thirteen years the plasma phosphatase varies between 3·0 and 10·0 units with an average value of 6·92.

Results

Phosphatase.—Taking the series as a whole, it was found that immediately after the fracture there was an increase in plasma phosphatase which fell to a minimum value at two or three weeks, after which time there occurred a secondary rise. This is best illustrated in patients with fracture of the femur. In this group the minimum value was obtained at

TABLE 1.

AVERAGE VALUES OF PLASMA PHOSPHATASE (UNITS) AND SERUM PHOSPHORUS (MGM. PER CENT.).

SITE OF FRACTURE.		1-3 DAYS.	6-8 DAYS.	14 DAYS.	21 DAYS.	28 DAYS.
FEMUR	PHOSPHATASE ...	11·4	9·7	7·4	6·5	11·9
	PHOSPHORUS ...	4·1	4·4	4·2	3·7	4·0
TIBIA	PHOSPHATASE ...	8·4	6·6	6.7	9·5	7·2
	PHOSPHORUS ...	4·5	4·7	4·2	5·0	—
HUMERUS ...	PHOSPHATASE ...	8·9	8·9	6·3	—	8·7
	PHOSPHORUS ...	4·6	4·8	4·0	—	4·4
RADIUS AND ULNA	PHOSPHATASE ...	11·6	6·5	—	—	8·0
	PHOSPHORUS ...	4·4	—	—	—	3·4
WHOLE SERIES	PHOSPHATASE ...	9·1	8·3	6·6	8·0	8·8
	PHOSPHORUS ...	4·4	4·6	4·1	4·3	4·0

three weeks and the secondary rise occurring after the third week was much more marked than in any of the other groups. Repeated determinations of plasma phosphatase were made in eleven patients. The results shown in table 2 indicate the tendency for the phosphatase value to be high shortly after the fracture, and thereafter to fall. Of the eleven cases in this group only two showed an increase at the end of one week; in all the others there was a definite reduction.

Two patients are not included in table 2 as estimations of phosphatase were not undertaken until some weeks after the fracture had been sustained. In one of these with a compound fracture of the left tibia, union was extremely slow and the plasma phosphatase remained low from the sixth to the ninth week. Mitchell[6] in cases with delayed union observed a sharp rise in phosphatase at the end of the first week but otherwise nothing to distinguish them from those in which union took place at the usual time. In the other patient with a fracture of the left radius that had united in a bad position the bone was broken and reset. This led to an immediate reduction of phosphatase from 8·0 to 5·7 units.

Calcium.—No significant changes were observed in the values for serum calcium.

Phosphorus.—Tisdall and Harris[8] found that serum phosphorus increased in value during the period of fracture healing and suggested that the absence of such an increase frequently heralded long delay in union. Mitchell[6], however, could not confirm these findings. In the present series, the figures obtained for serum phosphorus indicate that an increase takes

TABLE 2.

REPEATED ESTIMATIONS IN INDIVIDUAL PATIENTS.
(Phosphatase—units: Phosphorus—mgm. per cent.)

SITE OF FRACTURE.	NAME.		1-3 DAYS.	6-8 DAYS.	14 DAYS.	21 DAYS.	28 DAYS
FEMUR ...	J. McG.	PHOSPHATASE	11·1	8·4	—	—	13 3
		PHOSPHORUS	4·6	5·4	—	—	4·0
	J. L.	PHOSPHATASE	12·0	—	9·1	—	—
		PHOSPHORUS	3·8	—	4·2	—	—
	J. S.	PHOSPHATASE	10·7	—	—	7·8	—
		PHOSPHORUS	3·5	—	—	3·7	—
	W. O'D	PHOSPHATASE	11·9	6·7	—	—	—
		PHOSPHORUS	3·8	3·9	—	—	—
	W. K.	PHOSPHATASE	8·8	5·7	—	—	13·3
		PHOSPHORUS	5·6	5·7	—	—	—
TIBIA	H. M.	PHOSPHATASE	10·1	5·3	—	—	—
		PHOSPHORUS	3·6	3·9	—	—	—
	J. D.	PHOSPHATASE	8·8	—	—	10·5	—
		PHOSPHORUS	4·2	—	—	4·2	—
	M. P.	PHOSPHATASE	6·9	8·9	—	—	—
		PHOSPHORUS	4·8	5·8	—	—	—
	J. F.	PHOSPHATASE	5·9	3·7	3·9	—	—
		PHOSPHORUS	4·3	5·0	4·3	—	—
HUMERUS ...	M. H.	PHOSPHATASE	—	8·9	5·0	—	—
		PHOSPHORUS	—	5·1	4·6		
	W. D.	PHOSPHATASE	7·7	10·4	—	—	—
		PHOSPHORUS	4·2	6·0	—	—	—

place about one week after the injury. The averages at one week show a rise of 0·2 mgm. per cent. (table 1) but in individual cases (table 2) this figure is frequently exceeded. Hunsberger and Ferguson[3] observed that serum phosphorus and phosphatase values moved in opposite directions during the healing of fractures. Mitchell[6] could find no evidence of this inverse movement. The figures given in table 1 and 2 suggest, however, that there is some tendency for the plasma phosphorus and phosphatase to

move in opposite directions, thus resembling what takes place during the healing of rickets.

Site of fracture.—Table 3 shows that in the present series high values for plasma phosphatase tend to occur in fractures of the femur. Of seven cases with fractured femur examined within three days of the accident, five (70 per cent.) had a plasma phosphatase above 11·0 units. With fracture of the forearm bones the incidence of high values was four in ten, of the humerus three in nine and of the tibia only one in eleven. The results recorded for the present series resemble those obtained by Mitchell[6] in adult patients with multiple fractures, in whom the phosphatase was found to fall during the first two weeks and rise in the third week. In his patients with single fractures the phosphatase increased during the first week. It is possible that the more rapid increase in children is due to the fact that in this period of life growth is active, with a consequent increased tendency to form phosphatase.

TABLE 3.

SHOWING INCIDENCE OF HIGH PHOSPHATASE VALUES OBTAINED WITHIN THREE DAYS OF FRACTURE.

Site of Fracture.	Total Number of Cases.	Cases with Phosphatase above 11·0 units.
Femur	7	5
Tibia	11	1
Humerus	9	3
Radius	10	4

Summary

The plasma phosphatase and serum phosphorus and calcium were estimated in children at various intervals after a fracture injury. The plasma phosphatase appeared to increase within the first few days and thereafter to decrease. The serum phosphorus reached a maximum at the end of the first week. The serum calcium was not significantly altered. The change in plasma phosphatase was most marked in fractures of the femur.

Thanks are due to Dr. Noah Morris and Mr. Matthew White for suggesting this investigation and for their helpful criticism throughout.

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THE IRON-DEFICIENCY ANAEMIA OF LATE INFANCY

BY

HAROLD W. FULLERTON, M.A., M.B., CH.B.,
Beit Memorial Research Fellow,
Department of Medicine, University of Aberdeen.

Since attention was drawn by the work of Mackay[1] to the great frequency of anaemia during infancy, many investigators have studied the problem. As part of the large-scale investigation into the iron-deficiency anaemias of the poor classes, which has been carried out in Aberdeen [2, 3], haemoglobin estimations by the Haldane method have been made in 789 infants of all ages up to twenty-three months. A chart showing the course of the haemoglobin level according to age in 629 infants has already been published[3]. Since that time haemoglobin estimations of 160 infants between the ages of nine and twenty-three months have been made, and in figure 1 the results obtained in the complete series of 789 infants are presented. The figure at each point on the curve represents the number of infants available for calculation of the average haemoglobin level for each age. It is seen that a very marked fall in haemoglobin level occurs during the first two months of life, namely, from a level of 145 per cent. at birth to 77·6 per cent. at two months. This fall is due to rapid reduction by haemolysis of the polycythaemic state present in the foetus as compensation for the low oxygen tension in the placental circulation. Following the slight rise in average haemoglobin level during the fourth month, the curve falls gradually until the eighth month. Thereafter there is a marked change, the haemoglobin level falling from 78·5 per cent. at the eighth month to 69·6 per cent. for the ages, eleventh month and twelfth to seventeenth months. From this point onwards the curve shows a rise which continues throughout childhood[3] and which is probably due to the increasing iron content of the diet during this period.

The percentage distribution of decimal ranges of haemoglobin for each age group is shown in table 1. It is seen that the incidence of severe anaemia increases towards the end of the first year and continues to be high throughout the second year. The highest percentage of haemoglobin levels less than 60 per cent. in infants less than nine months of age is four, while for the age groups of nine months onwards the incidence of this degree of anaemia is 13, 9, 23, 16 and 12 per cent. respectively.

The course of the haemoglobin curve throughout infancy and the high incidence of anaemia from the ninth month onwards, are in agreement with the findings of several investigators. The difference between the haemoglobin levels of the infants examined in Aberdeen and the level of

86 per cent. (Haldane) which is deduced by Mackay to be normal for infants of the age group five to fourteen months, is a striking demonstration of the frequency of anaemia among infants of the poor classes in that city.

It is not proposed to consider all the variations in haemoglobin level which occur throughout infancy from birth onwards. Attention will be confined to the iron-deficiency anaemia of infants from the ninth month to the end of the second year. Moreover, this anaemia will be considered only on the basis of iron-deficiency, without discussion of the numerous other

TABLE 1.

PERCENTAGE DISTRIBUTION OF HAEMOGLOBIN LEVELS IN 667 INFANTS : 1 TO 23 MONTHS.

Age (Months.)	Number	Haemoglobin Range.										Average Hb.
		20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100–109	110–119	
1	12	0	0	0	0	0	42	8	8	25	17	90·8
2	50	0	0	0	4	18	36	28	12	2	0	77·6
3	49	0	0	2	2	16	39	27	12	2	0	77·1
4	62	0	0	2	0	10	34	34	19	2	0	80·5
5	50	0	0	0	0	10	36	48	2	4	0	79·8
6	61	0	0	0	3	15	46	31	5	0	0	77·9
7	48	0	0	2	2	4	52	35	4	0	0	77·4
8	37	0	0	0	0	8	43	43	5	0	0	78·5
9	66	0	1	0	12	12	44	26	5	0	0	73·8
10	56	0	0	2	7	27	36	27	2	0	0	72·7
11	62	0	0	2	21	19	40	16	2	0	0	69·6
12–17	97	1	0	6	9	23	44	12	4	0	0	69·6
18–23	17	0	0	0	12	35	41	6	6	0	0	71·5

factors which have been suggested as of etiological importance, e.g., deficiencies of copper[4, 5, 6], manganese[7] and other metals, and of vitamin C[8, 9]. The part which these other deficiencies play in disorders of haematopoiesis has been rendered prominent by the results of animal experimentation, but their effect in humans is far from certain. The haematological characters of the common anaemias of infancy and the excellent results of treatment with iron preparations containing only insignificant traces of other metals[10], point unmistakably to iron deficiency as the factor of paramount importance.

Etiology

The etiology of the iron-deficiency anaemia of late infancy may be discussed under four headings (1) the type of milk feeding, (2) the effect of maternal iron deficiency, (3) the birth weight, and (4) the effect of infections.

The type of milk feeding.—It has been clearly shown by Mackay[1] that the type of feeding has an influence on the haemoglobin level in infancy. This conclusion is verified by the findings here presented in table 2. For

TABLE 2.

AVERAGE HAEMOGLOBIN LEVELS ACCORDING TO THE TYPE OF FEEDING.

Age (months)	1	2	3	4	5	6	7	8	9	10	11	12	13	14-16
Breast-fed ...	83.6 (7)	(8.2 34)	78.2 (23)	77.0 (23)	87.7 (30)	78.2 (25)	80.3 (20)	85.5 (11)	75.6 (28)	74.2 (18)	73.7 (19)	73.1 (17)	71.8 (14)	72·7 (10)
Mixed feeding	—	77.8 (6)	87.5 (4)	81.0 (15)	77.8 (11)	77.9 (18)	77.6 (15)	76.3 (16)	71.4 (19)	73.6 (24)	69.0 (21)	69.1 (7)	71.0 (6)	72.0 (3)
Bottle-fed ...	89 3 (3)	73.6 (5)	71.5 (4)	84.0 (10)	73.5 (2)	74.6 (8)	71.5 (8)	73.2 (5)	67.1 (9)	65,8 (12)	68.1 (16)	60.5 (11)	65.2 (12)	57.0 (4)

The figures in parenthesis represent the number of cases.

purposes of classification, ' breast-fed ' infants comprise those in whom breast feeding was continued for at least eight months; ' mixed feeding ' signifies breast feeding for at least one month, with artificial feeding during the rest of the period; and ' bottle-fed ' infants are those who were artificially fed throughout or who were breast-fed for less than one month. It is seen that from the age of five months onwards, the average haemoglobin levels of the breast-fed infants are higher than in those who received ' mixed-feeding,' and considerably higher than in ' bottle-fed ' infants.

While it is generally agreed that such differences are due to the higher iron content of human milk and the greater degree of ' availability ' of this iron, there is a lack of data sufficiently reliable for a quantitative assessment of the difference between feeding with human and with cow's milk. In a previous communication[11] it was estimated that the iron contained in human milk during the first six months of lactation was approximately 180 mgm. On this basis 240 mgm. may be taken to represent the iron intake of an infant during nine months' breast feeding. Figures for the iron content of cow's milk[12, 13, 14, 15] are for the most part considerably lower than those for human milk, but they show such marked variation that the calculation of an average figure would be of little value. Moreover, very few iron-balance experiments have been carried out in infants fed on breast milk and on cow's milk. Josephs[16] found a positive iron balance of 6 mgm. per mensem in infants fed with cow's milk. Retentions of a similar magnitude were found by Langstein and Edelstein[17] in babies fed with human milk, but only two experiments were performed on infants more than a few days old. On the other hand, Blauberg[18] concluded that the iron retention in infants fed with human milk was five times greater than when cow's milk was used.

On the basis of the calculations presented under the next heading, the blood iron content of an infant of nine months with a haemoglobin level of

70 per cent. is approximately 270 mgm. The difference in average haemoglobin level between breast-fed and bottle-fed infants of this age is approximately 3 per cent., according to the figures of Mackay. The data here presented show a greater difference but the number of cases is smaller than in Mackay's series. A difference in haemoglobin level of 3 per cent. where the blood iron is 270 mgm. is equivalent to 11·6 mgm. iron. From what has been said, it appears quite probable that the total iron retention

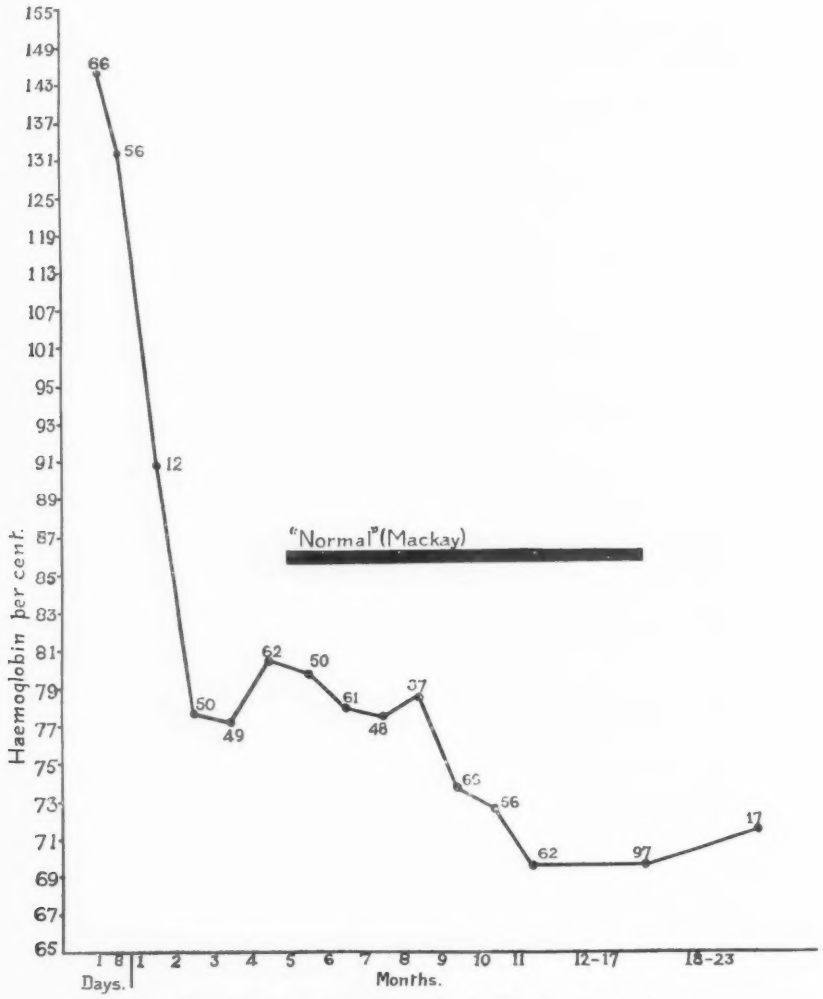

FIG. 1.—Average haemoglobin levels during infancy.

in breast-fed infants during the first nine months of life may exceed that of artificially-fed infants by such an amount. Hence if this difference in iron retention is reflected quantitatively in the haemoglobin level, the lower haemoglobin concentrations of ' bottle-fed ' infants are readily explained.

In summary, it may be said that, although reliable data are insufficient for definite conclusions to be drawn, the greater degree of anaemia present in artificially-fed infants is probably due to a low iron retention. It should,

however, be observed that this theory does not explain the fact that in Mackay's series the artificially-fed infants showed lower haemoglobin levels than breast-fed infants at all ages from birth to thirteen months. It will be shown later that, in the absence of increased loss of iron from the body, iron deficiency does not occur in infants of average birth weight in the early months. This is exemplified by the present findings, for in table 2 it is seen that only from the fifth month onwards is there a consistent difference in the haemoglobin levels of breast-fed and artificially-fed infants.

The effect of maternal iron deficiency.—It is generally agreed that maternal anaemia does not influence the haemoglobin level of the infant at birth[19, 20, 21]. The results obtained in 65 infants within twenty-four hours of birth and in 47 infants on the eighth day, support this conclusion (table 3).

TABLE 3.

AVERAGE HAEMOGLOBIN LEVELS OF INFANTS ON THE FIRST AND EIGHTH DAYS ACCORDING TO MATERNAL HAEMOGLOBIN LEVEL.

Maternal Hb.	85+		75—84		74 and less.	
Age (days)	1	8	1	8	1	8
Average Hb.	143·3	130·1	144·0	133·6	148·1	131·1
Number	17	12	31	20	17	15

It is the view of many authorities[1, 20, 22, 23, 24] that infants born of anaemic mothers become anaemic towards the end of the first year. The explanation usually given of this late development of anaemia in the infant, is that pregnant women suffering from iron deficiency supply inadequate liver stores of iron to the foetus, and that early exhaustion of these stores follows the milk feeding period of early infancy. It appears that the attractive nature of this hypothesis has rendered its acceptance general, although the scientific evidence in its favour is very scanty.

Bunge[25] was the first to stress the importance of the liver stores of iron at birth. He showed that the liver iron-content of new-born animals was proportionately much greater than in adults and presumed that in infants prolonged milk-feeding would result in anaemia after exhaustion of the iron stores of the liver present at birth. Also, the fact that anaemia occurs in the second and third generations of rats fed on an iron-poor diet[26, 27] is often adduced as evidence that maternal iron deficiency results in the development of anaemia in the offspring. Such results have been applied by many workers to an interpretation of the anaemia of infancy, without regard to the fundamental differences which exist between the iron metabolism of experimental animals and of humans. Rabbits increase their weight six-fold during the almost exclusive milk feeding of the first four weeks of life, and rats grow even more rapidly. An infant weighs approximately only two-

and-a-half times its birth weight at the age of nine months. It is obvious, therefore, that the demand for iron during the period of milk-feeding is relatively much less in the infant than in the rabbit or the rat. Consequently it cannot be deduced that the liver store of iron present at birth is of equal importance in humans and in animals. Morever, the relation of total foetal weight to maternal weight is much higher in experimental animals than in the human. For example, a female rat weighing 250 gm. has on an average a litter of eight or nine young with a total weight of 36 to 45 gm., giving a foetal-maternal weight ratio of 1:7 to 1:5·6. In the human the ratio is much less, approximately 1:16. Hence maternal iron deficiency is much more likely to result in foetal iron deficiency in rats than in infants. These simple calculations show clearly that inferences drawn from animal experimentation cannot be applied loosely to the study of the same problem in man.

The theory that maternal iron deficiency leads to a similar condition in the infant depends mainly on the experimental work on animals referred to briefly above, and on the investigations of Strauss[20], which have been widely quoted. Strauss found that all the infants of twelve anaemic mothers developed anaemia towards the end of the first year. It has been shown, however, that the occurrence of iron deficiency in infancy is dependent on many different factors, e.g., birth weight and the rate of growth, the type of feeding and the incidence of infections. Hence, unless a series of cases is sufficiently large to exclude variations in these factors, little importance can be attached to the results.

During the course of these investigations the correlation between maternal and infantile anaemia has been especially studied. Haemoglobin estimations were made as far as possible at the same time in 223 mothers and their infants of ages nine to sixteen months (series 1). In 113 cases (series 2) haemoglobin estimations of the mothers had been made also during

TABLE 4.

CORRELATION BETWEEN ANAEMIA IN MOTHERS AND INFANTS.

	Maternal Hb Ranges.	Infants: Ages 9–16 months.			
		Number.	Average Birth Weight.	Percentage Bottle fed.	Average Hb.
Series I.	85 per cent. +	86	7 lb. 7 oz.	25	70.6
	75—84 per cent,	43	7 lb. 7 oz.	32	68.6
	Less than 75 per cent.	38	7 lb. 0 oz.	58	70.6
Series II.	80 per cent. +	45	7 lb. 5 oz.	26	69.2
	70—79 per cent.	41	7 lb. 7 oz.	35	70.3
	Less than 70 per cent.	27	7 lb. 12 oz.	29	64.5

the pregnancy. None of the mothers or infants in these series had received iron therapy. In both series the mothers were divided into three groups,

'normal,' 'mildly anaemic,' and 'severely anaemic.' When haemoglobin estimations of the mothers were made from nine to sixteen months after the birth of the infant (series 1) the haemoglobin ranges are 85 per cent. and over, 75 to 84 per cent. and less than 75 per cent. In series 2 the ranges are 5 per cent. less for each group owing to the physiological hydraemia of pregnancy. In the infants the average haemoglobin levels have been calculated and are presented in table 4. In series 1 the infants of anaemic mothers show the same average haemoglobin level as the infants born of non-anaemic mothers. Series 2 shows that the average haemoglobin level is 4·7 per cent. lower in infants of anaemic mothers than in those of normal mothers. The significance of this finding is partly counteracted by the fact that the infants of normal mothers are slightly more anaemic than those of mildly anaemic mothers. Therefore serious doubts must exist as to whether either of these slight differences is significant.

It has already been pointed out that the other factors which tend to cause anaemia in infants must be controlled before deductions can be drawn from such investigations. Accordingly the average birth weight and the frequency of 'bottle feeding' have been calculated for each group and are included in the table. There is little variation in the average birth weight of the different groups, but it is interesting to note that in both series anaemic women were less often able to breast-feed their infants than non-anaemic women. This is a point which warrants further investigation. In summary, these results suggest that infants of anamic mothers are slightly, if at all, more liable to develop anaemia than those of non-anaemic mothers.

It is convenient at this stage to consider briefly the quantitative aspect of iron deficiency in infancy. It has already been pointed out that the haemoglobin level at birth bears no relation to maternal anaemia. The high haemoglobin level of new-born infants is generally agreed to be a compensation for the low oxygen tension in the placental circulation. The reaction of the human organism to low oxygen tension, e.g., in individuals living at high altitudes, appears to be two-fold, comprising polycythaemia and increase in blood volume[28]. Therefore, it is to be expected that the blood volume in infants is high. This question has been investigated by several workers[29, 30, 31]. Lucas and Dearing found that the blood volume of thirty infants not more than two weeks old varied over a wide range, but was, on an average, 14·7 per cent. of body weight. A decrease occurs during the first year of life, but the available data are insufficient to show the rapidity and extent of this fall. At one year the percentage blood volume still exceeds the figure for adults. Omission to consider the high blood volume during infancy, and particularly at birth, has led authors to adopt an erroneous conception of the iron metabolism of infants.

Taking 3·1 kilogrammes as the average weight, 145 per cent. (Haldane) as the average haemoglobin level, 14·7 per cent. of body weight as the blood

volume, and 50 mg. per cent. as the iron content of blood of 100 per cent. haemoglobin, it is found that the iron content of the blood at birth is:—

$$\frac{\text{Blood vol.}}{100} \times \frac{\text{Hb. per cent.}}{100} \times 50 \text{ mgm.}$$

$$\text{i.e. } \frac{31 \times 14{\cdot}7}{100} \times \frac{145}{100} \times 50 = 330 \text{ mgm.}$$

The accuracy of this figure depends mainly on the magnitude of the blood volume, and, since only few determinations have been made, and these show variation, the figure can be presented merely as an approximation. Nevertheless it may safely be deduced that usually at least 80 per cent. of the iron content of a new-born infant is present in the haemoglobin molecule.

Various figures are found in the literature for the non-haemoglobin iron content of the liver at birth. Gladstone[32] found an average of approximately 30 mgm., Sheldon 50 mgm.[33] and Toverud 60 mgm.[34]. It should be pointed out that in such investigations failure to obtain the liver in a blood-free state prior to analysis is probably frequent. This would tend to give results that are too high. For purposes of calculation, however, 50 mgm. will be taken to represent the average iron store of the liver at birth.

If the tissues of the infant, exclusive of blood and liver, contain the same proportion of iron as those of the adult (23 mgm. per kilogramme body weight)[35], it may be calculated that their total iron content is approximately 70 mgm. Josephs[36], as a result of experiments on rats, deduced that the tissue iron in the human was less than 5 mgm. per kilogram, but the figure adopted here is approximately in agreement with the findings of Hahn and Whipple in dogs[37]. Hence it may be concluded that the iron content of a new-born infant is distributed as follows:—

Blood	330 mgm.
Liver	50 mgm.
Other tissues	70 mgm.
Total ...	450 mgm.

A total of 450 mgm. is slightly in excess of the generally accepted figure[11], but it has already been observed that the figure for blood volume (14·7 per cent.) is based on relatively few results and it is obvious that a lower figure would reduce the blood iron. The above distribution of the iron content of the new-born infant may therefore be taken as approximately accurate.

It has been established that the iron released by the haemolysis which produces the rapid fall in haemoglobin during the first two months of life, is largely conserved[38]. This is shown by the balance studies of Josephs[16] and Langstein and Edelstein[17]; and Gladstone[32] has demonstrated that the released iron is stored in the liver. Apparently the total loss during the period of rapid haemolysis is very small, approximately 4 mgm.[16]. From the end of the second month onwards the infant is in a positive iron balance of approximately 6 mgm. per mensem[16, 17].

It is now of interest to apply these conclusions to an analysis of the iron content of breast-fed infants at the age of nine months. For this purpose calculations will be based on the following figures:—

Blood volume = 10 per cent. of body weight.
Body weight = 7·75 kgm.
Hb. (Haldane) = 86 per cent.

$$\text{On this basis the blood iron} = \frac{\text{Blood vol.}}{100} \times \frac{\text{Hb. per cent.}}{100} \times 50 \text{ mgm.}$$

$$= \frac{775}{100} \times \frac{86}{100} \times 50 \text{ mgm.} = 333 \text{ mgm.}$$

The iron content of the tissues (exclusive of the liver) may be calculated as having increased proportionately to the body weight, i.e., tissue iron $= \frac{775}{310} \times 70 = 175$ mgm. Hence the total iron content of the infant, exclusive of the liver iron store, is 508 mgm. It is apparent, then, that if the liver store of iron present at birth (50 mgm.) has been utilized for new haemoglobin formation, a retention of 58 mgm. over a period of nine months milk feeding is necessary for the maintenance of a haemoglobin level of 86 per cent. at nine months. From the discussion presented above, it would appear that retentions of this magnitude occur in breast-fed infants. Hence it may be concluded that in infants of normal birth weight an ideal haemoglobin level of approximately 86 per cent. should be attained at the age of nine months if the liver store of iron present at birth is completely utilized. It should be stressed that this calculation applies only to hypothetically ' perfect ' infants, that is, those who are of normal birth weight, are breast-fed, and who have suffered from no infections, gastro-intestinal upsets or even teething pyrexia prior to the haemoglobin estimation.

Although it is impossible to claim a great degree of accuracy in the above calculations, owing to insufficient information regarding blood volume changes and iron balances, it is clear that the important iron stores in the new-born infant are present in circulating haemoglobin and not in the liver. Indeed, if it is presumed that no liver iron reserve is present at birth and that this deficit of 50 mgm. is wholly reflected in a lower haemoglobin level, then the blood iron at nine months would be 283 mgm. (333 − 50 mgm.) which represents a haemoglobin level of 73 per cent. Obviously, therefore, a partial deficiency in the liver iron store present at birth can have only a slight effect on the haemoglobin level in later infancy. It may be concluded, then, that not only do these results fail to show any significant correlation between the common degrees of maternal iron deficiency and anaemias in late infancy, but also that the hypothesis generally upheld as

explaining such a correlation is unconvincing when examined on a quantitative basis.

The question may be considered also from the standpoint of the maternal iron content. The hypothesis under consideration implies that a woman with iron deficiency supplies to the foetus sufficient iron for a normal haemoglobin level, and, presumably, normal tissue iron at birth, a total of 400 mgm., but fails to supply the 50 mgm. which is the average liver store of iron; i.e., in the presence of iron deficiency the maternal organism always transfers to the foetus 90 per cent. of its normal complement of iron, but fails to transfer the last 10 per cent. necessary for liver storage, an amount which would result in an insignificant alteration in the maternal iron content. Such a theory is untenable. If maternal iron deficiency is reflected in the infant, probably it acts in other ways, such as a lowering of the blood volume. The evidence presented in a previous paper on the iron deficiency anaemias of pregnancy[39], showed that the iron drain of the foetus is not sufficiently large to cause a marked effect on the maternal iron content. Therefore, the iron content of the new-born infant is probably independent of that of the mother, except, perhaps, in the most severe degrees of maternal iron deficiency. In this connexion it is interesting to note that the infants of the eight mothers most anaemic during pregnancy (haemoglobin less than 55 per cent.) had an average haemoglobin of 65·5 per cent. when approximately one year old, i.e., less than 4 per cent. below the general average for this age.

Further support of these conclusions is afforded by the effect on the infant of iron treatment of the mother during pregnancy. Ferrous sulphate (nine grains a day) was taken during pregnancy for periods varying from one to four months by 56 of the mothers whose infants were examined when nine to sixteen months old. The effect of this therapy in a series of pregnant women, which included the 56 cases here considered, has been discussed in a previous communication[39]. It was shown that the haemoglobin levels of the iron-treated women rose during pregnancy and those of the non-treated women fell. The average haemoglobin level of the infants of 56 women treated during pregnancy was 70·3 per cent., while that of 167 infants whose mothers received no treatment was 68·8 per cent. All the infants were nine to sixteen months old at the time of examination. The average birth weight of the infants whose mothers received iron therapy in pregnancy was 7 lb. 9 oz., and 28 per cent. of the infants were artificially fed. The corresponding figures for the control group were 7 lb. 5 oz. and 34 per cent. Hence the slightly higher haemoglobin level of the infants of treated mothers may be due to the higher average birth

weight and the lower incidence of artificial feeding, and not to any direct effect of the iron therapy.

Birth weight.—The investigations of many authors have shown that infants of low birth weight develop an iron-deficiency anaemia[1, 16, 40, 41, 42]. The average haemoglobin levels of 222 infants of ages nine to twenty-three months, arranged according to birth weight, are presented in table 5. It is clearly seen that the lower the birth weight the lower is the haemoglobin level in late infancy. The discussion presented in the previous section makes the reason for this correlation evident. The smaller the infant at birth, the lower is the absolute iron content of circulating haemoglobin. Consequently, less iron is conserved following post-natal haemolysis, to be utilized in the new haemoglobin formation which accompanies growth. It should be emphasized, however, that this explanation depends on the fact that infants of low birth weight grow more rapidly in relation to birth weight than infants of normal weight. If this were not so there would be no greater tendency for the development of iron deficiency in infants small at birth, unless other factors such as increased susceptibility to infection were operative. The importance of the rate of growth in contra-distinction to the birth weight has been stressed by Mackay[1] and by Josephs[16].

TABLE 5.

HAEMOGLOBIN LEVELS OF INFANTS ACCORDING TO BIRTH WEIGHT.

Birth weight (lb.) ...	2	3	4	5	6	7	8	9+
Number of cases ...	2	—	10	8	32	47	51	16
Average Hb. ...	41·0	—	53·9	62·4	66·5	69.2	72·1	71·0

A hypothetical example makes it clear that a slightly increased rate of growth may result in a considerable reduction in the haemoglobin level. It has already been calculated that an infant weighing 3·1 kgm. at birth and 7·75 kgm. at nine months, should have a haemoglobin level of 86 per cent. at nine months if a liver store of 50 mgm. and a dietary iron retention of 58 mgm. are utilized for haemoglobin formation. The haemoglobin level of an infant similar in all respects except that the weight at nine months is 9 kgm. instead of 7·5 kgm., would theoretically be 68 per cent. In this calculation the tissue iron of the second infant is taken as representing the same relation to body weight as in the first infant. Therefore the haemoglobin level at nine months is 18 per cent. less when the weight at nine months is 2·9 times the birth weight instead of 2·5 times. Absolute accuracy cannot be claimed for these figures, but since the only respect in which the second infant differs from the first is in the weight at nine months, the effect on the haemoglobin level of an increase in rate of growth becomes evident.

Although the correlation between anaemia and low birth weight is well-marked, it should be realized that the factor of real importance is not

actually the weight but the total iron content which depends mainly on the blood volume. The correlation holds because the birth weight may conveniently be taken as a rough index of the total blood volume. Nevertheless the work of Lucas and Dearing[29] has shown that considerable variations in blood volume can occur irrespective of the birth weight. Hence it is possible that a new-born infant of 5 lb., with a high percentage blood volume, may have a higher total blood iron than an infant of 7 lb. with a low blood volume. This may explain why some infants of low birth weight maintain a high haemoglobin level in spite of rapid growth.

Since it is believed that the deposition of iron in the liver occurs especially during the last months of gestation[35], many authors consider that the iron-deficiency anaemias, so frequent in premature infants and twins, is due to exhaustion of liver iron stores which are deficient at birth. From what has been said with regard to the effect of low birth weight, it is clearly unnecessary to postulate such a deficiency. Moreover, it has already been demonstrated that a low iron reserve in the liver at birth can influence only to a slight extent the haemoglobin level in late infancy. With more accurate data than are at present available regarding the blood volume changes and the retention of iron throughout infancy, it would be possible to construct a table showing the expected haemoglobin levels at different ages, according to the weight of the infant at birth. In conclusion it may be said that the anaemias of premature infants and twins is a direct consequence of two factors—a low iron content at birth and rapid growth.

The effect of infections.—It is generally agreed that infections during infancy tend to cause anaemia. Nevertheless there appears to be a lack of statistical information on this point, and it is not definitely known whether certain types of infection cause a more severe anaemia than others. Mackay[1] believes that most slight infections do not influence the haemoglobin level, but that severe illnesses of many types, especially pyogenic diseases, are followed by anaemia. During the course of this investigation the history of illnesses suffered by the infants examined was obtained from the mother. In approximately fifty per cent. of the cases diseases of an infective nature had occurred. These were of various types, the most common being nasal catarrh, bronchitis, measles and otitis media. Analysis of the data is shown in table 6. It is seen that there is no significant difference between

TABLE 6.

AVERAGE HAEMOGLOBIN LEVELS OF INFANTS ACCORDING TO HISTORY OF INFECTIONS.

Age (Months)		1	2	3	4	5	6	7	8	9	10	11	12–17	18–23
No history of infections	Number	8	29	22	32	27	26	20	16	28	26	35	44	3
	Aver. Hb.	85.1	78.7	78.1	79.5	79.1	76.8	77.7	78.3	71.	73.2	70.3	69.2	78.3
History of infections	Number	1	13	7	18	14	21	20	14	29	22	22	39	3
	Aver. Hb.	71.0	78.8	80.3	82.7	82.6	80.3	97.5	77.0	74.6	72.6	70.5	67.8	72.0

the haemoglobin levels of infants with a history of infections and those of infants who suffered from no illnesses. Such a result is indeed surprising when it is realized that apart from the effect of infections in producing anaemia de novo, anaemic infants, according to Mackay, show a higher morbidity rate than non-anaemic infants.

The results of this part of the investigation may be criticized on several grounds. In the first place, the intelligence of the mothers was not high and it is probable, therefore, that they did not include mild illnesses in their account of the infants' health. The importance of this point will appear later when it will be shown that falls in haemoglobin level may accompany pyrexia due to teething, conjunctivitis and other mild infections. Secondly, the information was obtained at busy out-patient centres by a variety of observers, including unqualified health visitors. It is to be expected, therefore, that considerable differences existed in the care with which a history was elicited from the mothers. Finally, the period elapsing between an infective illness and the haemoglobin determination was in many cases unknown. Thus the investigation was uncontrolled in several respects. In order to check the reliability of these histories, health visitors were asked to make careful inquiry into the incidence of illnesses of all types in infants of the same social status as those discussed in this article. It was found that illness had occurred during the first year of life in 87 per cent. of 428 infants whose mothers were specially interrogated. This suggests that the failure to obtain a correlation between anaemia and infections may be largely due to the fact that almost all the infants had infective illnesses, although a positive history was given in less than 50 per cent of the cases. Nevertheless, if mild infections may cause anaemia, severe infections such as would be noted by mothers and health visitors should logically produce still more anaemia, and therefore, a correlation between haemoglobin levels and a history of illnesses would have been expected. The controlled observations to be described later leave little room for doubt that infections produce anaemia, and it is concluded that clinical data collected routinely by workers in busy out-patient clinics may be of little value.

Definite information regarding the rôle of infections is afforded by the result of an investigation carried out in an institution in Aberdeen. Twenty-six infants of ages six to twenty-two months were observed for approximately one year while under medical supervision and excellent dietetic and hygienic conditions. When the investigation began in December, 1934, the infants showed a wide haemoglobin range from 46 to 89 per cent. The average haemoglobin level was 67·2 per cent. and 26·9 per cent. of the infants were severely anaemic (haemoglobin less than 60 per cent.). In an attempt to estimate the therapeutic efficiency of small doses of ferrous salts, three grains of ferrous sulphate in tablet form was given daily to each infant, in divided doses. This treatment was in most cases continuous from January to May, 1935. Since it was found that many infants refused to swallow the tablets, a solution of ferrous sulphate in 50 per cent. glucose was made and given in doses of 1 drachm t.i.d. (total daily dose = 3 grains) from May to October.

The average haemoglobin levels of the infants throughout 1935 are plotted in figure 2. It is seen that after an initial rise in haemoglobin level from 67·2 per cent. to 79 per cent. during the first five weeks, a marked fall occurred and was followed by a slow and irregular rise. The lowest average haemoglobin level coincided with an epidemic of naso-pharyngeal and bronchial catarrh in late April and May, which affected practically every child in the Home. Whilst this may be taken as strong evidence that the epidemic was directly responsible for the low haemoglobin level in May, the fall of the curve in February and March, and the slow rise after the epidemic, still require explanation. It was found that in addition to the epidemic, infections of various types were present in individual cases throughout the year, and the course of the average haemoglobin level therefore does not reflect accurately the effects of iron therapy. Accordingly, the data regarding each infant were analyzed separately, and it became apparent that almost in every case infections had occurred after the end of January. Moreover, the haemoglobin level was lowered with unfailing regularity after each infection. The types of illness included broncho-pneumonia, otitis media, chicken-pox, tonsillitis and enlarged neck glands. It is not practicable to publish in detail the protocols of all the infants, but in figure 3 are shown five typical examples. Although haemoglobin estimations were made in each infant at approximately monthly intervals, for simplicity in presentation all of these values are not charted in the figure. In each case the course of the haemoglobin level during a period of infection is represented by a straight line joining the haemoglobin value obtained before the onset and the first value determined after the infection had ceased. A similar plan is followed in showing the course of the haemoglobin level during periods when no infection occurred. The marked falls in haemoglobin level during the course of infections are clearly shown. The curve B. K. illustrates the effect of two separate infections, each being accompanied by a fall in haemoglobin and succeeded by a rise.

In the case histories of three infants, pyrexia attributed to teething was noted. In each case the haemoglobin fell during the period of pyrexia, the extent of the fall varying from 4 per cent. to 21 per cent. In another infant conjunctivitis with pyrexia caused a fall in haemoglobin level of 10 per cent. These findings suggest that mild disturbances are accompanied by a fall in haemoglobin level. The results obtained from this investigation leave no room for doubt that infections of various types cause marked falls in haemoglobin level even during iron therapy. Moreover, no response to therapy may occur until several weeks after pyrexia has subsided.

The mode of action of infections in producing anaemia is not clear Probably iron deficiency is a factor, since it has been shown by Josephs[16] that a negative iron balance occurs during a period of infection. However, the rapid falls in haemoglobin level suggest that the toxins of infective processes cause, in addition, an inhibition of blood formation in infants.

Discussion

From what has already been said regarding the anaemia of late infancy, it appears that the following conclusions are warranted:—

(1) The iron content of the infant at birth is of great importance in determining the onset of iron deficiency.

(2) Breast-fed infants are less liable to anaemia than artificially-fed infants.

(3) The common infective illnesses of infancy produce a rapid fall in haemoglobin level and may inhibit blood regeneration for a considerable time after the disappearance of clinical evidence of infection.

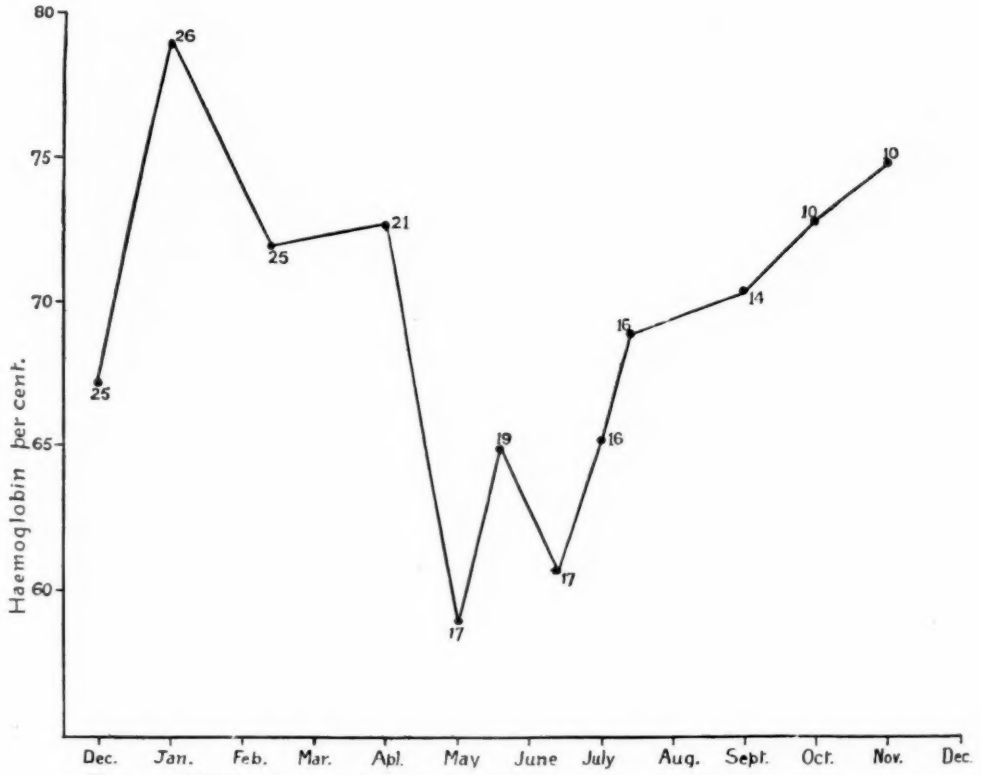

FIG. 2.—Effect of catarrhal epidemic on average haemoglobin levels.

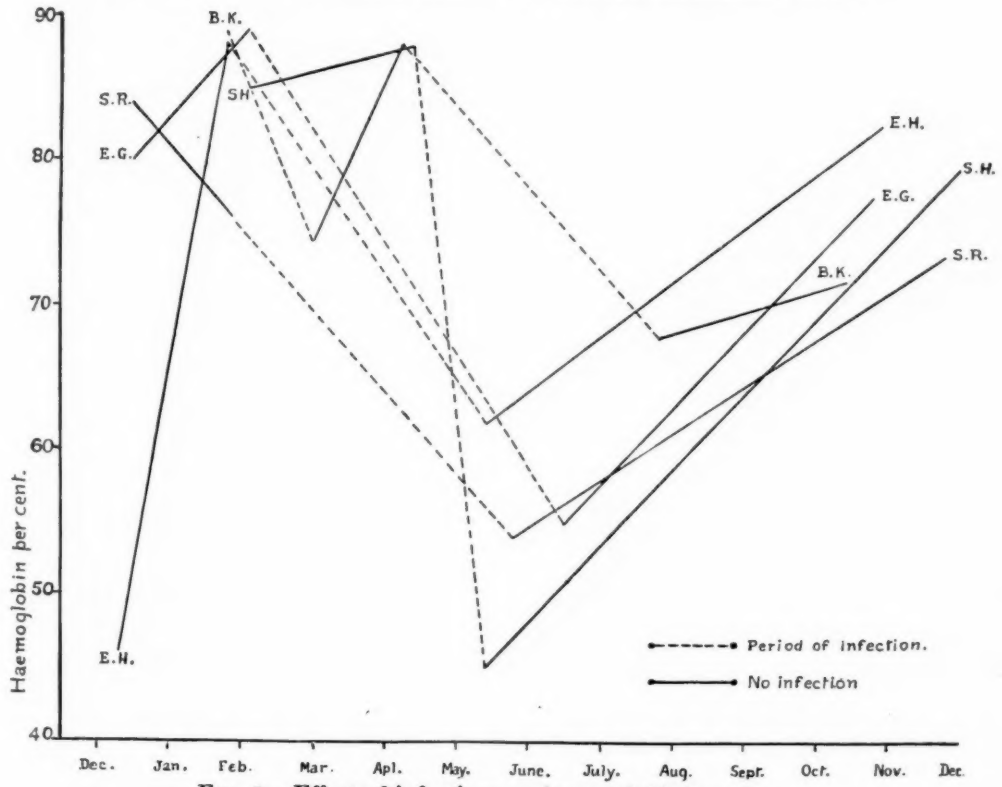

FIG. 3.—Effect of infections on haemoglobin level.

It has been indicated that a breast-fed infant of normal birth weight and free from all illnesses should not theoretically develop iron deficiency before the age of nine months. After this time the increasing iron content of the diet presumably should maintain the haemoglobin at a normal level. It has been clearly shown that this ideal is rarely attained by infants of the poor classes in Aberdeen. Actually only 13 per cent. of infants between the ages of nine and twenty-three months had haemoglobin levels of 80 per cent. or more. Therefore the factors causing anaemia must be prevalent in the class of infants examined. The incidence of low birth weight and artificial feeding has already been discussed, and it has been shown that a large proportion of the infants had suffered from infections. In an attempt to discover if other factors were of importance in determining the development of anaemia, analysis was made of the infants of ages nine to twenty-three months who weighed at least 7 lb. at birth, were breast fed for not less than eight months and who, according to the histories given by the mothers, had no infections during four months prior to examination. Only 56 infants fulfilled these conditions and of these 8 (14·3 per cent.) had haemoglobin values less than 70 per cent., and 2 (3·6 per cent.) were less than 60 per cent. Therefore, whilst the incidence of anaemia is much less in this group than in the complete series, it is still sufficiently high to lead to the suspicion that factors other than those considered may play an etiological rôle. The explanation of these cases of anaemia may lie in one or other of the following possibilities:—

(1) Recent work has indicated that achlorhydria is of fairly frequent occurrence during infancy and plays an important part in producing iron deficiency[44, 45, 46]. It is therefore possible that achlorhydria was present in some of the anaemic infants in whom no other etiological factor was found.

(2) It has already been emphazied that the birth weight gives only an approximate estimate of the iron content of the infant at birth, owing to the large variations in percentage blood volume which occur. Hence, some of the infants of normal birth weight who developed anaemia may have had a low blood volume.

(3) The unreliable nature of the histories of the infants, as given by their mothers, has already been discussed, and it has been observed that infections regarded as mild might have been overlooked.

(4) It is probable that the type of diet given to infants after weaning varies within wide limits in regard to its iron content. Hence some cases of anaemia during the second year may be due to a low dietary iron intake.

The anaemia discussed in this communication is frequently called the 'nutritional anaemia of infancy,' and many cases in which the etiological factor of importance is low birth weight or infective processes, have been erroneously classified under this heading. The quantitative aspect of the iron metabolism in infancy indicates that a deficient iron intake during the first nine months has not a marked effect on the haemoglobin level. On the basis of the figures already presented, it may be calculated that an infant of average weight, haemoglobin level and blood volume at birth, will attain a

haemoglobin percentage of 71 at the age of nine months, when no dietary iron has been retained during this time. However, as growth continues, a deficient dietary iron intake becomes of increasing importance, and possibly many cases of severe anaemia during the second year are attributable to this factor. There is, however, little information regarding the absolute and ' available ' iron contents of the diets of infants after weaning, and the degree of variation in different classes of the population has not been clearly established. Therefore the importance of a deficient iron intake in infancy can be at present only a matter of conjecture. It ought to be emphasized, however, that anaemia should be explained on the basis of deficient iron intake only in cases where the birth weight was normal, and where no infections have occurred; and it should be borne in mind that severe anaemia due to dietary deficiency alone is unlikely to occur during the first year. There is, therefore, usually little justification for applying the term ' nutritional ' to the common anaemias of infancy.

The frequency of anaemia in infancy has led to the suggestion that the dietary regime commonly adopted in this country should be altered by the introduction of iron-rich foods in larger quantity and at an early age. The advisability of such a change is a matter for paediatricians to decide. Certainly, from the standpoint of iron deficiency alone, there is no necessity to institute drastic dietary revisions. Medicinal iron, when properly prescribed, is taken without difficulty by infants, and the effects of such therapy on haemoglobin regeneration are likely to be more satisfactory than any that could be obtained by dietary measures. The great frequency of anaemia in infancy, and the knowledge of its etiology which has been gained in recent years. suggest that a haemoglobin estimation should be made in all infants at the age of three months. Where such a procedure cannot be carried out, a course of iron therapy should be given routinely at the age of three months to all infants of birth weight less than 7 lb., and in cases of artificial feeding. Moreover, iron therapy should be instituted after illnesses of an infective nature, and should be continued for at least two to three months. Such measures would undoubtedly effect a marked improvement in the health of infants, since iron deficiency increases susceptibility to infective illnesses and may cause retardation of growth. A point of practical importance which should be borne in mind is the difficulty of diagnosing anaemia in infants without actual estimation of the haemoglobin percentage. This applies particularly to infants who are regularly placed in sunshine and fresh air. For example, the general appearance of the infants examined in the institution mentioned above often belied the low haemoglobin values which were found.

An attempt to obtain a series of haemoglobin estimations in infants of the upper classes was found to be impracticable owing to the difficultties

accompanying most investigations of such a nature on private patients. It is, however, of interest to estimate theoretically the incidence of anaemia in infants of the upper classes, by assessing the probable frequency of the etiological factors discussed above. It is clearly established that the diet of the mother has little or no effect on the birth weight of the infant except in cases of the extreme malnutrition which occurs in times of war and famine[47, 48, 49]. Several investigations have revealed no significant correlation between the birth weights of infants and social class[50, 51, 52]. It may be deduced, therefore, that the incidence of anaemia due to low birth weight alone is similar in the upper and lower classes. Probably the incidence of infections is less in infants of the upper classes, and the dietary regimen after weaning is in most cases more satisfactory. In this connexion it is of interest to note that the incidence of anaemia among the infants in the institution already described was greater than in the large series of out-patient infants. Such a result is surprising in view of the fact that the standard of the dietary regimen and the general management of the infants in the institution is certainly much higher than in poor class infants, and probably excels that of babies of the better classes. It is possible that this finding may be explained by a higher incidence of infective illnesses among infants congregated in an institution.

In conclusion it may be said that whilst anaemia is probably less frequent in infants of the upper classes, it should nevertheless be regarded as of real importance and the rules already laid down for the institution of iron therapy should be observed.

Conclusions

1. Subnormal haemoglobin levels (haemoglobin less than 80 per cent. Haldane) were present in 87 per cent. of 298 poor-class infants between the ages of nine and twenty-three months.

2. The common anaemia of late infancy is due mainly to iron deficiency which is dependent on low birth weight, artificial feeding and infective illnesses.

3. Probably infections have the additional effect of producing inhibition of blood formation.

4. Anaemia in infancy depends only to a slight extent, if at all, upon the common degrees of maternal iron deficiency.

5. The incidence of anaemia among infants of the better classes is probably somewhat less than among the poor.

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DELINQUENCY IN RELATION TO THE BROKEN HOME

BY

R. G. GORDON, M.D., D.Sc., F.R.C.P.Ed.
(From the Bath Child Guidance Clinic.)

A considerable interest has recently arisen in the question as to why young people take to crime. To desire to find simple explanations for problems, and to discover rule-of-thumb methods whereby difficulties may be solved is an all too common tendency. It is also true that once such a simple explanation has been found, and such a rule-of-thumb method evolved, the problem loses its fascination and the solution its interest. There is not the least chance of such a loss of fascination and interest in the case of delinquency, for there are no simple explanations and no rule-of-thumb methods of solution. As William Healy emphasized and as many thinkers before him have realized, the delinquent is an individual and must be studied as such, and in the study of delinquency the mistake must not be made of fixing interest on the delinquency to the neglect of the individual who is delinquent. Stealing is probably the commonest delinquency in children, but stealing may be due to a host of causes and may require all sorts of different treatments, and when a young thief is under consideration, it is impossible to say that such and such a set of circumstances have arisen, or that such and such a line of procedure is going to prevent him stealing again. Therefore in presenting a paper on delinquency in relation to the broken home, I wish to explain quite clearly, that I do not regard the broken home as the cause of delinquency, or even perhaps as a cause of delinquency, but merely as a contributory factor among many, all of which have a hand in determining asocial acts. The deliquent must be studied in relation to his environment, and in any situation what contribution he has made and what contribution has been made by the environment have to be considered. It may be taken as axiomatic that both make a contribution, but that in different circumstances the relative value of the two contributions varies. I am inclined to think that if a long series of delinquencies in children be taken, it will be found that the contribution of environment apparently preponderates, and that if it is possible to change the environment in a suitable way, then the individual is capable of adapting to the more suitable environment, and no more trouble ensues. It must be admitted, however, that this may be due to the greater plasticity in adaptation which is enjoyed by the child compared with the adult.

Of all environmental factors, the broken home is recognized as one of the most important, and it is necessary to understand how this factor works.

First of all what is meant by the broken home? It can be defined as follows: whenever the normal relationship between the father, mother, child or children is disturbed, either by the absence of one or both parents or the intrusion of others into the circle, then the home may be described as broken. Thus, the situation will arise if either parent is dead, divorced or separated, or if step-parents or even step-children or adopted children are introduced into the home. The same situation will arise when the child is subjected to divided loyalties, as for example, when he spends a large part of his time living with an aunt or grandmother and the rest of his time at home with his parents.

Case records

The following cases may illustrate the influence of such a broken home.

1. Margaret was thirteen years old when first seen. On examination she was underdeveloped and rickety, with a depressed sternum and knock knees. She was of average intelligence and presented no signs of severe emotional instability except that she suffered from nightmares occasionally, but these were not serious. She was one of three children in the household all by different mothers. The step-mother stated that ' Margaret gets worse every day, she has been stealing from me at home and always telling lies. I don't know what to do. I persuade her in every possible way, she wants to be carried about, she sleeps badly and has nightmares, she takes no notice of what me or her father says.' The school report was good, except that the child was frequently late. The child's explanation of being late from school was that she was so busy doing household work, she could not get there in time. She was asked what she did in the mornings and the following was the story: ' Washed and had a cup of water, laid breakfast for father, made my own bed, picked up ashes and polished grate, washed, cleared and washed up father's breakfast things, polished the table, laid the other breakfast things, made large bed and two small beds, changed and cleaned my shoes, combed my hair, had a cup of hot water, went over the living room floor with the floor duster, prepared and came to school.' Before starting the school day apparently the only breakfast was one cup of cold water and one cup of hot water. This was only the child's unsupported statement and must not be taken too seriously. The father and step-mother referred to their minister of religion for a character. According to him they were poor but admirable people. On closer examination this opinion seemed to be founded on the fact that after the birth of the step-mother's own child, the man had wished to leave her, but the minister had persuaded him to marry her, and since then they could do no wrong. Meanwhile, in spite of assertions from the parents that Margaret was looked after well with loving care, had had everything they could manage to give her, she, a growing girl of rising fourteen, continued to lose weight. As she went on getting thinner, she was taken into hospital for investigation; this proved entirely negative so far as organic disease was concerned, but she gained nine and a half pounds in weight in nine days. The ward sister reported: ' She takes her food well. Is a happy and contented child (before admission was sullen and morose). She made no complaints of either cruelty or deliberate neglect at home, but states that the family is sometimes so late in the morning that there was no time for breakfast.' After discharge, it was arranged that she should have dinners at the school canteen, but in spite of the greatest pains taken in trying to get her there, she soon ceased

to attend. On enquiry it was found that her father forbade her to go, as he required her at home to do household work. After this even the minister had to admit that the husband continually quarrelled with the wife and wanted to leave her; the home was neglected and Margaret again progressively lost weight. Eventually he pursuaded the father to allow Margaret to go to a residential school. A recent report from this school states: ' Health good, scholastic attainments average—said to be a good girl at school, needs to concentrate more. General intelligence average. Conduct good, on the whole making progress. Is a bright happy girl, general improvement in every way since coming here. She takes kindly to household duties and in all probability will be able to take a post in domestic service when of suitable age.' Such is the story of Margaret, a starved household drudge in a home where there was continual strife. It is scarcely surprising that she stole from her step-mother.

2. Robert, aged seven on first examination, was the illegitimate son of a woman now married to the father of her second son who only achieved legitimacy by two days. The family lived together in poor surroundings in complete disharmony. Robert was evidently a bone of contention between the parents, for they were both anxious to get rid of him, but the mother was the chief mover as she accused him of begging and pilfering on several occasions, and although he no doubt did steal, her statements could by no means always be substantiated. Robert was an unpleasant looking youngster, with defective articulation and obvious adenoids. These were removed but without much effect. His intelligence quotient was 80, i.e. he was backward but not legally defective. He was in homes during the first six years of his life and only came to live with his mother and step-father after this. The latter made some efforts to control the boy but these were not successful, and there were always outbreaks of bad behaviour. The boy himself was subject to periodic outbursts of temper, accompanied by lying, stealing, truancy and so on. Between these attacks he was only fairly good. In this connexion, it is interesting to record four reports from teachers at about nine-month intervals.

> February, 1929. He is amenable to discipline, anxious to please, timid, no moral defects.
>
> November, 1929. Not amenable to discipline, not affectionate, spiteful, destructive, pilfers, has undesirable personal habits.
>
> July, 1931. Not amenable to discipline, not affectionate, spiteful, destructive, bullies, steals, in and out of school, lies, very objectionable in personal habits (exposes himself).
>
> March, 1932. Amenable to discipline, fairly obedient, affectionate, easily led, not destructive, not bad tempered, not aggressive, of rather solitary habits.

From these reports by different teachers is clearly seen that his behaviour is erratic, but there is a definite suggestion that this erratic behaviour may owe something to the influence under which he was living at the time. He was most certainly not wanted at home and was a most unprepossessing child. It was not surprising that he had outbursts of aggression in which he ran counter to everyone. He was eventually brought before the juvenile court for sleeping out for six nights. He was put on probation, but soon broke this and was sent to a residential school.

3. Peggy was the daughter of a school teacher, ambitious that the child should also enter the profession and perfectly conscientious and kind, but perhaps not very devoted to his daughter. Her own mother had died when she was an infant, and for the first nine years of her life, she had lived

with aimable but elderly grand-parents. Her step-mother was also a teacher and was a conscientious woman, who did her best for the child. Peggy had a few epileptic fits in childhood and was subject to outbursts of temper. She had an intelligence quotient of 107. She gained a scholarship to the secondary school, but was brought to the clinic at the instance of the head mistress when she was fifteen, because she was not getting on, and she did not seem likely to be fitted for the profession of a teacher. She was sullen and morose, would not do the lessons which she did not like. It seemed impossible to appeal to her in any way, and she seemed to have no affection for anyone. Even at this stage a bad prognosis was given. She was of the egocentric epileptic personality, for whom the only appeal is the hedonistic one. That is to say, if a thing hurt her she might be dissuaded from doing it, and if it gave her any real personal pleasure, she might be induced to take an interest and give her mind to it. She was obviously, a person who could never make a teacher, From this time she deteriorated, she lived for herself alone, would do nothing for anyone and became quite impossible. She reduced her parents to despair with her tempers, her sulks and her utter selfishness. The grandparents quite unjustly laid the blame for this state of affairs on the step-mother, so she was sent to them. In six weeks she was back home, having completely worn out and defeated the old people. After this, matters rapidly reached a crisis and she became suicidal, on one occasion swallowing 40 cascara tablets which she had cunningly secreted. Fortunately, she was sick and no great harm was done, but the conclusion was reluctantly reached that the only thing to do was to certify her under the Lunacy Act, although she was only seventeen. This case is quoted in contrast with the preceding two, to illustrate that the broken home even if it exists, is not necessarily the cause of trouble. Here was a child incapable of giving or taking affection and however loving her parents had been, it would have been no different. The trouble was inherent, the blame lying in some antecedent defect of stock, and not with the child's contemporaries.

4. Joan was an illegitimate child living with her mother, step-father and two step-sisters younger than herself. For some time she had been brought up by her aunts, who were peculiarly foolish people, praising her if she was sly or cute or even dishonest, and losing no opportunity of blackguarding the child's mother in her presence. Lately she had left these aunts and gone to live with her mother. She was subject to attacks of wilful disobedience, temper and unkindness to her small step-sisters. She was referred to the clinic by the headmistress of her school, who complained that although she was reasonably quick in school (her I.Q. was 91 per cent.), she was untidy in manual work, and although usually amenable to discipline, was at times spiteful and disobedient. She pilfered small sums of money, both at home and in school. She had gained a scholarship for a senior school, but had failed to maintain this, owing to refusal to work. Physically, she was undersized for her age, and for this reason, unable to maintain her status in games with girls of her own age. In this case, there is no doubt that several influences were at work. Her aunts had prejudiced her against her mother, and had encouraged her in sly, underhand behaviour, such as easily led to pilfering. Her step-father was quite well disposed towards her, but he did not take a great deal of interest in either her or his own children, and although he was quite willing to cooperate, he was foolish and played off the aunts against his wife in the child's regard and on one occasion threatened that the child would go to a lunatic asylum if she did not behave. Joan was definitely jealous of her step-sisters and this sometimes broke out into active bullying. Above all she resented her smallness which she felt kept her among the babies. Treatment consisted in eliminating the foolish

aunts from her life with the co-operation of father and mother to whom Joan's particular difficulties were explained. She was given thyroid and pituitary gland extract to promote her growth and she not only grew in physical stature, but in self reliance and self respect. After leaving school her mother reported that she was a perfectly normal girl and a real help in the home. The latest report was that she was in work, doing well and giving no trouble.

5. A not dissimilar story, but less satisfactory is that of Dennis a sharp precocious boy with an I.Q. of over 107. He lived part of the time with his father and step-mother, a younger step-brother and sister, and part of the time with his aunt and her friend. At first the main trouble with Dennis was truancy from school, which was largely because he was not sufficiency interested, and the work to which he was set was far too easy. Later however, he got into trouble with his step-mother and was said to have stolen money from her. His father entirely failed to control him and his truancy became serious. It was never easy to get reliable information, his first school authorities were not helpful, largely owing to suspicion that religious prejudice was behind the complaints. The step-mother did not want him and complained of every sort of delinquency and spitefulness directed by the boy against herself and his step-sister. The father was weak and did not exert himself to find a solution. For a time he was sent to stay with an aunt, a well-meaning woman. She was out at work all day and had no love for her sister-in-law—the boy's step-mother. The result was that she had no control of him and as she abused his step-mother in front of this extremely sharp boy, he soon learnt to make capital out of this, and ran home to retail what the aunt said about the step-mother, and then proceeded to the aunt to tell her the counter abuse. Naturally this did not make for peace but the excitement of it all went to the boy's head. School, where his lessons were easy and in no way interested him, could not compete, he truanted more and more and it was obviously only a matter of time until he got into serious trouble. So far as the boy was concerned, there was no particular psychological peculiarity about him, and it seemed reasonable to suppose that if he could only be subject to kindly discipline and control all would be well. The trouble was that the boy was approaching fourteen and after that age could not be sent to a Home Office residential school, which seemed the best solution in the circumstances. In the absence of funds, the only way to achieve this was by bringing him before the courts, but his only crime was truancy, and the only person to accuse him of pilfering was his step-mother, in whose word no one put very much credence. The police, however, found him sleeping out and charged him with wandering. The magistrates agreed to send him to a residential school from which the reports as to his behaviour are at present good, and I have some confidence that he will make good, but with the reservation to which I shall refer later.

Discussion

It is proposed to review these five cases and consider what contribution the broken home had to make to each. In the first case the home had almost everything to do with the problem for Margaret was an average normal child, when she was not being starved and overworked. In the second case I think the contribution may be held to be about even. Robert had a bad home, he was not wanted and was never cared for, but he certainly was not normal himself. In the first place, he was intellectually backward, but not more so than many other members of society who give no trouble.

Secondly, he was physically of the adenoidal, rickety type, but again not more so than many other children of his age and station, and thirdly he was subject to periodic outbursts of temper and delinquency, which some are inclined to call epileptic equivalents, without knowing exactly what is meant by this. Yet there is something in the term and this periodicity of abnormal behaviour almost certainly owes something to a constitutional factor, of which the nature is as yet unknown. It may be concluded that it is doubtful if Robert would have made good in any environment, and it is doubtful if the most careful psychological treatment combined with a good environment, would have had much effect.

In the third case, Peggy, there appears to be no doubt. The influence of the broken home was negligible, and in her case there was an inherent incapacity for social adjustment and environment or treatment would have had no beneficial effect, because there was no straw out of which to make bricks. Such a personality frequently goes with epilepsy, and has been called by Pierce Clarke and McCurdy the epileptic personality.

In the fourth case, Joan, there was again a mixed influence. The house and the divided loyalties between aunts and mother were responsible for a good deal, and she was undoubtedly jealous of the step-sisters, who probably really found more favour in her step-father's eyes than she did, though this was not particularly noticeable to the outside observer. A potent factor was her undoubted grievance over her small stature and puny physique, a factor which is commoner and more important in boys than in girls. When this remedied itself in the course of nature and perhaps with the help of the gland preparations, she made a good adjustment.

The fifth case Dennis is one of peculiar interest. Here the home conditions, divided loyalties and jealousies, had a great deal of influence, but here was a boy of more than normal intelligence, full of the spirit of adventure, who found his ordinary surroundings dull and quite insufficient to meet his requirements. He was heading towards making the sort of young criminal who has lately been figuring in the newspapers to a considerable extent; the smash and grab raider, the rioters of Dartmoor and so on. It is hoped that he has been caught young enough and sent to a school where, while subjected to discipline, he may at the same time find occupation to interest him and extend him both mentally and physically.

Remedies

Let it be clear then that the broken home comes into the story of many delinquents and these five cases have only been taken at random as illustrations, but it must be remembered that there are plenty of children in broken homes who are not delinquent, and plenty of children in homes which are not broken who are delinquent, so that this factor is only one of many. There are many homes which are so unsatisfactory that the children ought to be got out of them. For this purpose the Public Assistance Committee may step in and send the child to one of their cottage homes, or to foster

parents. If the child enters them quite young, the cottage homes under a good matron are often quite successful, but they are of little use for those who have to be removed from their own homes at a later age. Foster parents sound all right in theory, but in practice the right people do not want strange children, and those who are attracted by the small payment which goes with the child are not as a rule the right people. There remain the various voluntary boys and girls homes, training ships and the residential schools, many of which have some free places. There are not enough of these, however, and it is difficult to get children into them. Some contribution is generally required and it is not usual for the parents in the homes here being discussed to be able or willing to afford this. With regard to the residential schools, the ordinary entrance to these is through the courts. Either the child must be charged with a crime or the parent must come to the courts complaining that the child is out of control. With regard to the latter point many parents are too lazy and indifferent to trouble to do this. Others not without reason feel that it implies a criticism of themselves and are therefore unwilling to take this step. Moreover magistrates are quite rightly chary of relieving a bad parent of all responsibility for his child, and placing this responsibility on the taxpayer. Under the Children's Act there is a clause under which the Education Authority has power to take action and bring a child before the courts. In the circumstances which have been described, and if this power is wisely used and administered, many of the difficulties may be solved. There remains crime as a means of entry to these school, but if the child is to benefit by the residential school, he must be sent there early, and the public are often unwilling to charge a child for petty delinquencies, so that he fails to come before the court until he has done something really bad, which is a culmination of a long series of asocial behaviour. Even so, many magistrates regard this as a first offence and put the child on probation either because they have no knowledge of his social and home surroundings, or in a few cases because the magistrate, though he obtains advice from those who know, rejects it because he thinks that he is being interfered with and that the advisors are trying to teach him his job. Probation is an excellent system in its proper place and under proper conditions, but when the home is quite hopeless and no co-operation can be expected from the parents, the probation officer does not have a chance, and it is not fair to burden him with such cases.

CASE REPORTS

SPONTANEOUS PNEUMOTHORAX OF THE NEWLY-BORN

BY

PHILLIP E. ROTHMAN, M.D.

(From the Hospital of the Good Samaritan, Los Angeles, California.)

Twenty-one cases of pneumothorax of the newly-born have been recorded in medical literature. A recent review by Glaser and Landau[1] emphasized the rarity of the condition, the high mortality, the greater incidence in the male sex, the predominance of left-sided involvement and the difficulties that arise in an attempt to explain satisfactorily the origin of this interesting and unusual complication. Willi recognized three groups of cases, classified according to their etiology, as mechanical, infectious, or congenital.

The first group includes such causative agents as forcible artificial respiration, the use of the Drinker respirator, obstruction of the air passages by aspirated amniotic material, enlargement of the thymus and collapse of the epiglottis. The exact significance of obstruction to the ingress of air in the production of a pneumothorax is by no means as obvious as certain writers suggest. Many cases of obstruction accompanied by the most laboured inspiratory efforts have been observed in cases of congenital laryngeal stridor, subglottic stenosis and other malformations of the upper respiratory passages without the escape of air into the pleural cavity. A recently observed case of obstruction due to aspirated amniotic material showed at autopsy a few marginal emphysematous bullae but not a pneumothorax notwithstanding very strenuous inspiratory efforts for several hours before death. It appears as a possibility at least, that histological studies of serial sections may disclose congenital defects in the lung tissue as the primary cause and mechanical obstruction to the entrance of air as a necessary but secondary factor in the development of this type of pneumothorax.

Three cases have been placed by Wilkinson[2] in the infectious group. He demonstrated conclusively in his own case that the formation of a pulmonary abscess which ruptured into the pleural cavity was caused by multiple septic pulmonary emboli and was not secondary to a low grade inhalation pneumonia starting at birth, a mechanism suggested by other investigators. The emboli were attributable to a septicaemia originating in all likelihood from an omphalitis or a circumcision wound. Unfortunately knowledge of neonatal septicaemias is still imperfect. Their occurrence has been noted in

the absence of any focus of infection and irrespective of the best obstetrical and nursing care.

The third group due to congenital pulmonary defects is best illustrated by Weiner's case. This child had a left pneumothorax, first noted fourteen days after birth. At autopsy a canal was found about the diameter of a pencil and communicating both with the pleural cavity and a bronchus. The canal opened a short distance from the surface of the lung within a fold of tissue which accounted for its valve-like action.

In approximately thirty per cent. of the cases recorded, no acceptable hypothesis could be advanced to explain the pneumothorax.

Clinical record

The following case observed at the Hospital of the Good Samaritan apparently belongs either to this group or to the cases with congenital defects. The mother was delivered by caesarean section and the baby

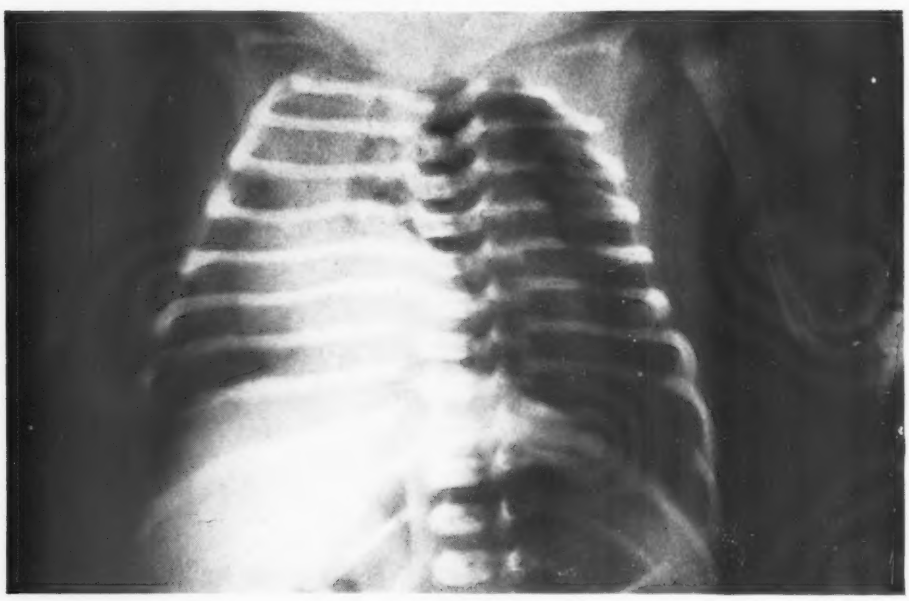

FIG. 1.—Left pneumothorax, heart and mediastinum are displaced to right.

weighed 8 lb. 1 oz. Pregnancy had been entirely normal and the operation under spinal anaesthesia was uncomplicated. Two siblings are living and well. A miscarriage preceded the last pregnancy. The infant's first inspiration was vigorous and his cry strong. His condition immediately after delivery presented nothing remarkable. A few minutes later respirations appeared slightly laboured and were accompanied by moderate cyanosis. It was thought that some mucus had been aspirated into the upper respiratory passages as a result of the initial inspiratory effort. The mucus present was

more than customary but not enough to cause obstruction. A five per cent. carbon-dioxide-oxygen mixture was administered through a funnel shaped mask in the usual way with a fairly satisfactory response. When the baby was stimulated the cry was lusty and the general condition at that time was not critical. Twenty hours after the birth, cyanosis had become marked and the dyspnoea moderately severe. Complete absence of breath sounds over the left lung was ascribed to atelectasis. Oxygen administration was begun and continued by nasal catheter. A second examination, five hours later, revealed dextrocardia in addition to the atelectasis. Since an uncomplicated true congenital dextrocardia is asymptomatic, the physical signs in this case were thought to be due either to a left diaphragmatic hernia with compression of the lung by intestine and consequent cardiac displacement, or to a left pneumothorax. The latter appeared more probable, as suppression of breath sounds was complete and the tinkling sound of air in the intestines was not elicited over the left thorax. X-ray examination confirmed the diagnosis of left pneumothorax and also showed a small pneumothorax on the right side. Oxygen was discontinued during the x-ray examination and the cyanosis immediately increased. The nasal catheter was re-inserted with obvious and convincing beneficial results. As the result of oxygen administration improvement was so satisfactory that aspiration of air did not seem warranted.

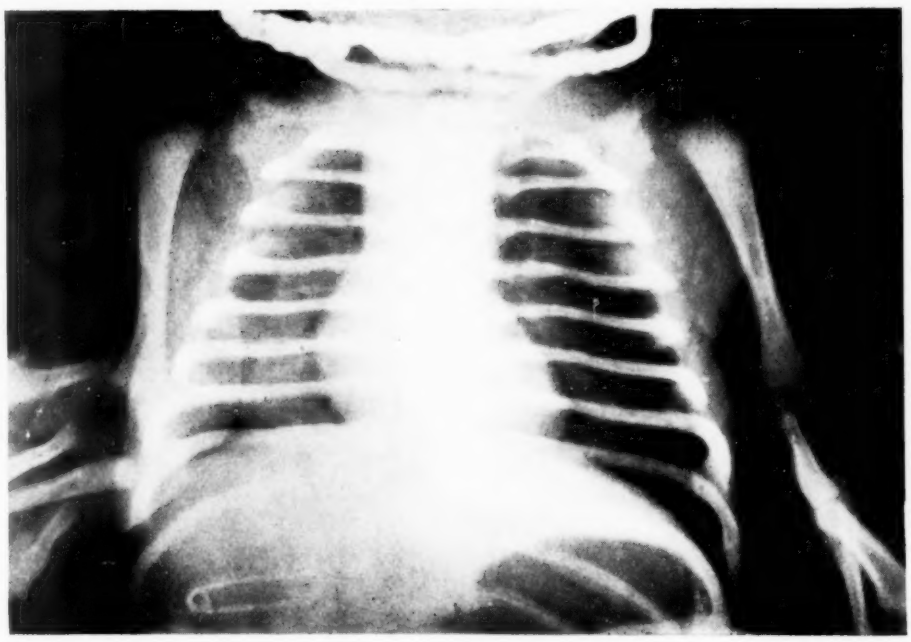

FIG. 2.—Complete disappearance of pneumothorax three days later.

Feeding was started and taken unusually well. The following day respirations were less laboured and at the end of the third day air was entering the left lung. On the fourth day complete expansion of the lung together with a normal position of the heart was verified by x-ray. At present the child, seven months old, is perfectly normal.

Summary

A case of pneumothorax of the newly-born with initial symptoms shortly after birth is presented. The cause could not be attributed to either a mechanical or an infectious factor. The administration of oxygen was the only therapeutic procedure used. A spontaneous recovery ensued.

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CONGENITAL ABSENCE OF THE PECTORAL MUSCLES

BY

E. D. IRVINE, M.D., AND J. B. TILLEY, M.D.
(Blackburn).

The four patients described in this paper exhibit congenital absence of the pectoral muscles in varying degree, and illustrate many points of interest. Three of them were observed during routine and special medical examinations of approximately 15,000 elementary school children, and one was a pre-school child in hospital: it is interesting to note that Scheslinger, according to Rector[1], discovered five cases in 54,000 patients.

Case 1 was discovered during the examination of a boy aged ten, the second of four children, who complained of cough: he is under observation

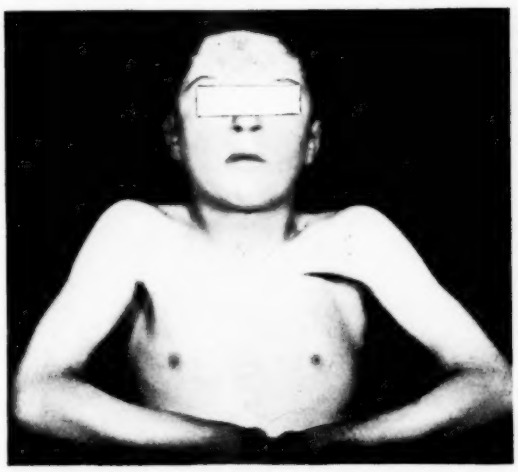

FIG. 1.

as a tuberculosis contact. The sterno-costal portion of the left pectoralis major and the left pectoralis minor are both missing. Although not previously noted, this is believed to be a congenital defect. The clavicular head of the pectoralis major is well developed and arises from the inner half of the clavicle; the deltoid is not hypertrophied (fig. 1). When the arms are extended above the head, a well-marked fold of skin running vertically across the axilla to the second left rib and interspace can be seen and in

the fold fibrous tissue can be felt deep to the skin: whether this is simply fascia or a vestigial or degenerated muscle is not known. He suffers no functional disability. X-ray examination of the chest reveals no bony abnormalities; he shows no other congenital defects and none are known in other members of his family.

Case 2 in a girl aged fourteen, the eldest of six, was first detected during a routine school medical examination five years ago; the general musculature and subcutaneous fat are well developed and when the child is at rest the defect is hardly evident though the skin of the left anterior axillary fold is puckered up, and the left breast is slightly elevated. Almost the whole of the sterno-costal portion of the left pectoralis major is missing and though it is difficult to be certain of this, the left pectoralis minor appears also to be absent. The persistent part of the major muscle is well developed and is attached at its proximal end to the inner third of the clavicle and the inner end of the first rib. There is no abnormal skin fold in the axilla and the deltoid is not hypertrophied (fig. 2). The child suffers no functional disability and seems otherwise normal. No congenital defects are known in the other members of the family.

Case 3 in a boy aged four, the younger of two children, was found during his stay in hospital. He suffered from septic pharyngitis and tonsillitis following pneumonia and the muscles generally were markedly atonic. The parents had previously observed that ' there was something one-sided about his chest.' The left pectoralis minor is absent, and of the major muscle only the clavicular head, arising from the inner third of the clavicle, and a slip attached to the inner end of the first rib persist. There is no functional disability, scoliosis or hypertrophy of the deltoid, and there is no abnormal skin fold in the axilla (fig. 3). No other congenital defects have been observed in him and none are known in other members of his family.

Case 4 is in a girl now aged five years, the third of five children. The mother states that ' the labour was precipitate and the right side of the chest was noticed soon after birth to be sunken in, and this side has never developed as the other has done.' She suffered from whooping cough as a baby and has bronchitis. The defect is obvious at a glance (fig. 4). The sterno-costal portion of the right pectoralis major and the right pectoralis minor are missing. There is a distinct indentation in the upper and outer part of the right chest in front and here the second and third ribs feel almost as if fractured. The clavicular head of the pectoralis major is well developed and arises from the middle third of the clavicle (a similar attachment of this part of the muscle has been observed clinically in normal children). When it is made to contract, a fold of skin can be seen beneath it suggesting the presence of underlying muscle, though none can be felt. The right nipple is elevated. When the right arm is extended above the head a fold of skin, in which can be felt what appears to be fibrous tissue, is evident on the right side extending from the axilla to the second intercostal space near the sternum. The child is otherwise well developed and she suffers no functional disability; there is no scoliosis and no hypertrophy of the deltoid. No other congenital defects can be found in her and none are known in the other members of the family. The skiagram (fig. 5) shows the deformity and narrowing of the upper part of the chest due to abnormality of the second and third ribs, the bony parts of which are ill developed, thin and short, that of the second rib being particularly short; it appears that ossification of the bodies of these ribs has failed anteriorly. No other skeletal defects are shown.

FIG. 2.

FIG. 3.

FIG. 4.

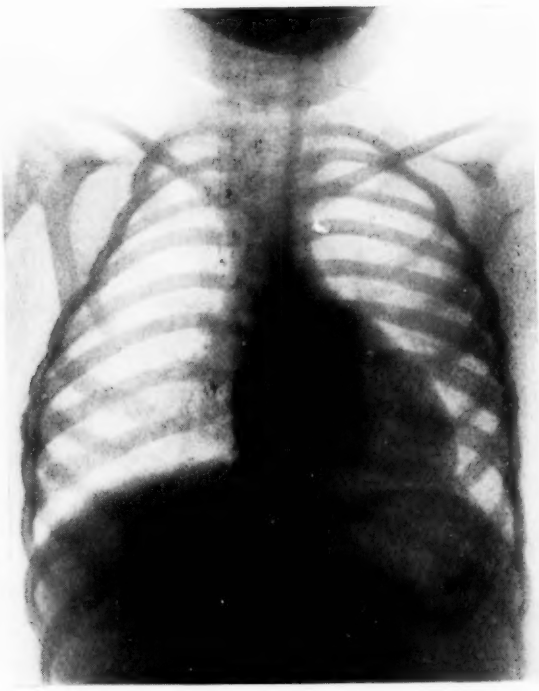

FIG. 5.

Discussion

Congenital absence or defect has been recorded of many muscles, the most frequently affected being the pectorals (Bing[2]). The apparent frequency with which these are affected as compared with other muscles has been in part ascribed to ease of ascertainment during routine clinical examination[3], but, as defects of the pectorals usually cause little or no functional disability and are often unnoticed by the patients or relatives—in only two of the present four cases had the relatives observed any abnormality—their comparative frequency may be even greater than Bing suggested. Such abnormalities are almost invariably partial and also unilateral: in the majority of cases the sterno-costal part of the pectoralis major and the whole of the pectoralis minor are absent; fewer show absence of the sterno-costal part of the pectoralis major alone, and only one case of absent pectoralis minor alone (detected in a man during mastectomy) has been described[4]. There may be associated abnormalities of the upper ribs or of the breast and nipple on the affected side, and sometimes other congenital defects co-exist. Scoliosis may be present. When only the clavicular portion of the pectoralis major persists it is, as a rule, together with the deltoid, much hypertrophied[3], and generally the patient suffers little or no incapacity. Alstead[5] described in his case, a fold of skin running across the axilla of the affected side suggesting the existence of a vestigial muscle. According to Rector[1] only one instance of the defect as an hereditary or familial manifestation has been recorded. In diagnosis the possibility of muscular dystrophy has to be remembered.

Lewis[6], from studies of the development of the pectoral muscles in human embryos, believed that a partial explanation of the abnormalities found in them may lie in a failure of the pectoral muscle mass to attach iteslf to the ribs or clavicle; he attributed the frequent association of absence of the pectoralis minor with absence of the sterno-costal portion of the pectoralis major to their early fusion (prior to differentiation).

Thanks are due to Mr. C. Haydock of Queen's Park Hospital, Blackburn, who has made the prints and to Mr. T. J. Shields, Librarian of the British Medical Association, for his assistance in regard to the references.

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A CASE OF THE KLIPPEL-FEIL SYNDROME

BY

JOHN THOMSON, M.B., CH.B., D.P.H.

(Late Assistant Medical Officer of Health, Fife County Council.)

Clinical record

This child, a girl, born 4.11.27, was seen at school medical inspection in December, 1934. Birth had been normal and she was breast fed for six months. She cut the first tooth at ten months, spoke the first single words at eighteen months, first walked at twenty-one months and first walked without falling at two years and seven months. Soon after birth it was observed that:—1. The head was tilted to the left side. 2. Strabismus was present. 3. The mouth was drawn up and to the right.

The child was seen as an out-patient at the Royal Hospital for Sick Children, Edinburgh, on three occasions, 2.10.29; 27.6.31; 7.6.33. She was an in-patient in the hospital from 14 to 25.7.31. It was observed in hospital that:—1. The neck was very short and stiff. 2. The head was thrust forward and to the left. 3. Left sterno-mastoid and left trapezius were shortened, grossly thickened and hard almost to the extent of feeling ossified. 4. There appeared to be some wasting of the scapular muscles. 5. Bony asymmetry of the face was present, the left side being smaller. 6. There was a cervico-dorsal scoliosis. 7. The child was weak, small for her age, slow in grasping things with her hands. 8. There was some weakness of the left arm and leg. 9. There was some paresis of the left side of the face, of the external rectus, and the left levator palpebrae. Subsequently, this paresis cleared up. 10. There was also slight left sided enlargement of the heart with a systolic murmur of maximum intensity a quarter of an inch outside the left sternal border, at the level of the nipple. This also cleared up.

An x-ray photograph taken on 17.7.31 shows (see fig. 1):—1. The seventh cervical vertebra has the tip of its spine fused with those of the

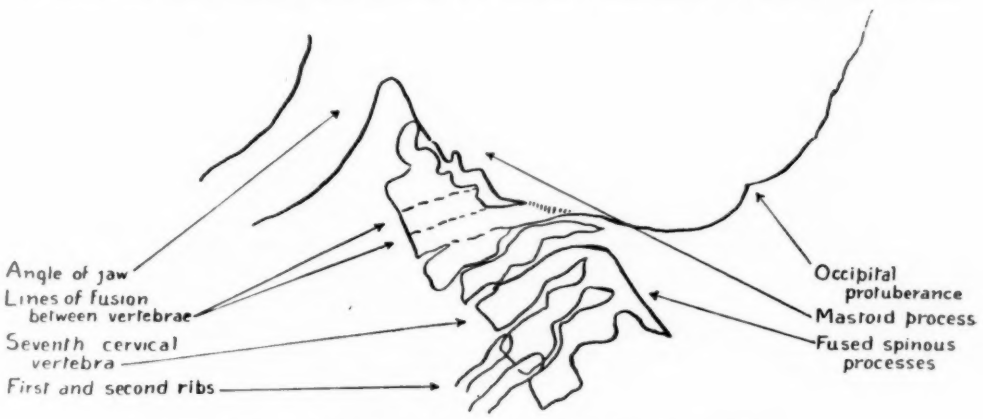
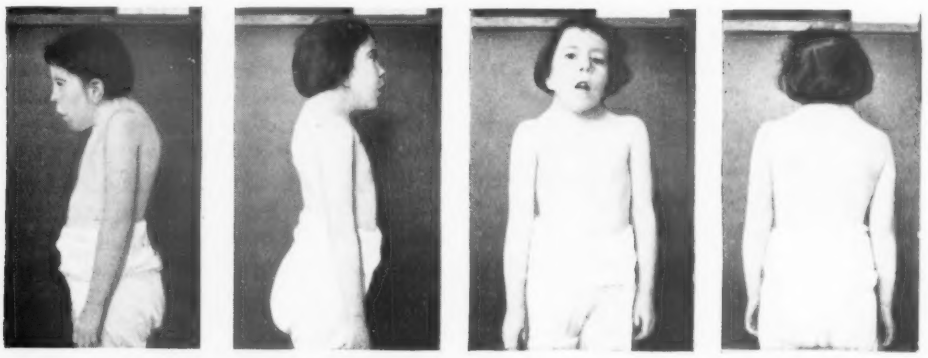


FIG. 1.—Drawing from skiagram taken on 17.7.31.

first and second thoracic vertebrae. 2. The sixth cervical vertebra is flattened from above downwards and has its body fused to the fifth cervical vertebra above. 3. The bony elements representing the fifth, fourth, third and second cervical vertebrae are displaced forwards by a quarter of an inch, and are fused together. Their common fused spine is in contact with the base of the skull, one inch in front of the occipital protuberance. 4. The odontoid process of the second cervical vertebra is fused to the posterior aspect of the anterior transverse arch of the first cervical vertebra.

Condition at beginning of treatment

On March 18, 1935, remedial exercises, with posture training and massage were begun. Hyperextension of the spine twice a day for half an hour with the hands clasped behind the head was also practised at home. The appearance of the child at the beginning of her treatment is shown in fig. 2A.



A B C D

FIG. 2.

The following typical signs are seen:—1. Short neck with low hair line and nuchal depression. 2. Kyphosis. 3. Position of head with upward look of the eyes. 4. High scapulae with some winging obscuring the curve of the spine. 5. Open mouth. In addition there was present, 6. Facial asymmetry and torticollis. 7. Contracture of all neck muscles, especially sterno-mastoids and trapezius. 8. Webbed neck. 9. Only slight head movements. 10. Elevation of left shoulder. 11. Mouth breathing.

It was also observed that whilst bimanual synkinesia was not present as it is classically described, complete dissociation of the movements of the hands had not been attained; e.g. when the child buttoned up her coat with the right hand alone, the left hand and fingers especially, were in a state of constant motion, as though they might be also handling buttons. Educationally, the child was backward. She attended at the orthopaedic clinic regularly as an out-patient, three times a week, and despite her educational backwardness proved to be an apt pupil.

Her posture and general carriage improved tremendously as will be seen from fig. 2B taken in September, 1936. The range of movement in the spinal column as a whole was greatly increased, while the strength and tone of the spinal muscles was vastly improved. Head movements also increased slightly. Educationally too, the child has improved. The other signs of the condition are naturally unaffected by the treatment.

Discussion

This condition, as originally described by Klippel and Feil[1, 2, 3], was stated to consist of (1) a numerical variation of the vertebrae; (2) more or less fusion between the bony elements of the cervical vertebrae; (3) accompanied sometimes by spina bifida or other congenital abnormalities.

So far some seventy to eighty cases have been reported in medical literature. Although the first detailed description, including post-mortem findings was given by Klippel and Feil, the first case recorded appears to be that of J. Jackson Clarke[1]. He instances ' a boy aged 4 yr. who from birth had had the head fixed so that the chin was close to the sternum and there was no movement in the cervical spine. The personal appearance recalled cases of anencephaly.' At about the same time as Klippel and Feil published their detailed findings of the condition, Meisenbach[5] reported a case of absence of the cervical spine. This nomenclature however, though it is used by many subsequent writers, is inaccurate, since in no case is the cervical spine completely absent. A further monograph on the subject was published by Feil in 1919[6], and since then a number of cases have been recorded. These are for the most part in the French literature, but cases are reported from Italy, Germany, Roumania (Vaselescu and Niculiscu[7]), Russia (Kroll[8], Yankelevich[9]), Scandinavia (Elowson[10]), and a number are reported in the English literature by American and British writers (Baumann[11], Greenberg[12], Willard and Nicholson[13], Mitchell[14], Clarke[1], Foggie[15]).

Etiology.—The cause of this condition has not yet been defined. All that can be said is that the condition is essentially an intra-uterine one. It is natural to look for a primary defect in the osseous system, but the frequent presence of mental defect as well as certain nervous phenomena, of which bimanual synkinesia[11, 13, 14, 15], is the most striking, show that the nervous system is not free from suspicion. The cause of this disturbance of the mesoderm or of the embryonal skeletal axis is open to speculation. Both disease of, and a low vitality of, the germ plasm have been offered as an explanation.

The condition does not appear to be a hereditary one, although Foggie[15] calls attention to the fact that Feil reports a case of the condition occurring in father and son; Kallius, of its occurring in father and daughter; Sicard and Lermoyez, of it occurring in a mother and three of her children.

Symptoms and signs.—Of these the most prominent is the short neck. So much is this so, that in Germany the condition is known as ' Kurzhals.' In France it goes by the name of ' les hommes sans cou '; and in this country it has been referred to as ' brevi collis.' As a result, a low hair line is seen at the back of the neck, and there is a distinct depression to be seen at the nape of the neck. It is referred to as the nuchal depression. The shortness of the neck is exaggerated by a kyphosis which is present in the dorsal region. The scapulae tend to be higher than usual and this also is exaggerated by the kyphosis present. The head is thrown forward and it appears as if the bony skeleton were not able to support it, for in extreme cases the chin may actually rest on the thorax. The head movements are of necessity limited. There is a degree of muscle spasm present in the cervical muscles. It is explained as being due to the muscles requiring to

take the place of the osseous system in supporting the head (Baumann[11]). There is a flattening out of the trapezius muscles giving rise to a broad appearance of the neck, and this is referred to by some writers as webbed neck. Torticollis is frequently present, and although facial asymmetry is not always obvious, its presence is not uncommon. Disturbance of the breathing may be present in the form of an obstruction, thus giving rise to the typical facies seen in adenoids. There may also be difficulty in swallowing. Spina bifida may be present, also bimanual synkinesia, deaf-mutism, disturbance of ocular movements, and various other congenital defects in different parts of the body, e.g. direct communication between the two ventricles of the heart. Some of these other congenital defects may be incompatible with life, and indeed of Mitchell's[11] six cases, two so affected died, one aged five weeks, and one aged six weeks.

Differential diagnosis.—The condition must be differentiated from Sprengel's shoulder, ordinary wryneck and tuberculosis of the vertebrae. There should be little difficulty in differentiating from Sprengel's shoulder, but it is confessed that the condition has been treated surgically as an ordinary wryneck. When this was done, no benefit accrued to the patient. The differentiation from tuberculosis of the vertebrae may not be so easy. The presence however of:—(1) Shortness of the neck—so short that the thorax reaches almost to the head—referred to by Klippel and Feil as the 'cervical thorax'; (2) the broadness of the neck; (3) the low hair line; (4) absence of pain; and (5) muscle spasm should differentiate the two conditions. Mention should be made here however that Yankelevich[9], has reported a case in which tuberculosis of the vertebrae co-existed.

Treatment.— In Jackson Clarke's case it is stated that 'operative treatment followed by massage gave to the boy a short neck with all the natural movements.' There is, however, no indication of the nature of the operative treatment carried out. Baumann[11] states, 'The deformity is stationary and not affected by treatment, it is disguised only with difficulty, and does not become less conspicuous as the patient develops.' Greenberg[12] says, 'therapeutic expectations are absolutely nil.' Other writers do not touch upon the question of treatment at all. It would appear, however, that despite the somewhat pessimistic pronouncements of some writers concerning the treatment of the condition, the present case tends to show that some improvement may be looked for: even when there is a degree of mental defect present, always provided that it is not such as to cause failure to secure that co-operation which is so necessary between the patient and the masseuse in carrying out this treatment. Whether the result of such treatment will be of permanent benefit or not remains to be seen. This patient is still under observation, being seen about once a week, during the school term.

Thanks are due to Prof. Charles McNeil for permission to peruse and make use of the notes of the case, and also the x-ray film, made when the child was in the Royal Hospital for Sick Children, Edinburgh.

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CEREBRAL SINUS THROMBOSIS IN CHILDREN

BY

J. H. EBBS, M.D., D.C.H.,

The Children's Hospital, Birmingham.

Thrombosis of the cerebral venous sinuses has been recognized for many years. The first description is credited to Morgagni[1] in 1717, and Abercrombie[2] made the first accurate study of the condition. It is usually classified as primary or secondary. The primary type is described as occurring with marasmus, dehydration, gastro-enteritis and anaemia; whereas the secondary type is always associated with infection, chiefly of the middle ear and mastoid region, and although it is a not uncommon sequel of infection spreading from the face, scalp, skull bones or meninges, it rarely follows trauma to the skull. Recently Ehlers and Courville[3] have described a combined type which is found in marantic, dehydrated infants with otitis media. Holt and McIntosh[4] state that, 'it is customary to distinguish between inflammatory or septic thrombosis and a so-called marantic or cachetic type. In the former, obvious inflammatory changes are found in the thrombus; in the latter, evidences of inflammation are inconspicuous. Infection in some part of the body is always present, however, and even here it is probably of etiological significance.'

Byers and Hass[5] give a complete review of the subject while reporting fifty cases which had been observed in Boston during a period of six years. They found twenty-six cases associated with infection and twenty-four which they classified as primary, one half of the latter occurring in August, September and October. Sixteen of the twenty-four cases showed a severe unexplained diarrhoea. Acute dehydration was a more important factor in these cases than malnutrition. Wyllie[6] has described three cases at the Hospital for Sick Children, Great Ormond Street, two of which were associated with pneumonia and one with infantile diarrhoea. He classifies the origin of the disease as otitic and marantic. The latter group includes those cases secondary to infantile diarrhoea, prolonged suppuration, tuberculosis, carcinoma, pertussis, chlorosis, empyema, pneumonia, appendicitis, cerebral tumour, infectious diseases and following operations. Ehlers and Courville[3] have reviewed the literature and have collected sixty cases of primary thrombosis of the internal cerebral veins. In the majority the thrombosis of the internal cerebral vessels was associated with a similar condition of the cerebral venous sinuses. Twenty-one of these cases occurred in infants or children. Simpson[7] analyzed forty-two cases of thrombosis of the cerebral vessels which had been found at the Hospital for Sick Children, Toronto, during a period of ten years. Some text-books of diseases of children do not mention the condition, whilst others refer only to thrombosis associated with mastoid infection. Some state that symptoms may be entirely lacking, the condition being found post mortem

in association with some other process. The usual picture described, however, is one of marked septic symptoms, i.e., chills, high temperature, headache and meningeal signs. Osler[8] described the syndrome of mental dullness, headache, convulsions, vomiting and paralysis. If the superior longitudinal sinus is affected paralysis of the legs may be the diagnostic point since the cortical supply to the legs is close to the superior longitudinal sinus. Recovery rarely occurs under these conditions and when it does a permanent spastic paralysis of the legs usually results.

Thrombosis of the cerebral vessels in children is not usually considered as a common occurrence, but during the past two years fourteen patients have been admitted to the Birmingham Children's Hospital suffering from this condition. The records of the hospital for the previous twelve years show that only eighteen cases had been found. It would therefore appear that there has been an increase in the incidence of the disease, but it still remains as an entity which is seldom considered in the differential diagnosis of cerebral conditions in young children. It is important if possible to diagnose the condition during life, and a review of several recent cases brings out many points which have been found of some value in achieving this end.

Case records

A summary of the age, etiology and important clinical and pathological findings has been made of the thirty-two cases recorded in this hospital during a period of fourteen years (table 1). The case records of eight patients are appended, and the fourteen cases observed in the past two years form the basis of the remarks which follow.

Case 19. M. O., a girl, aged two years, was well until two days before admission, when she became restless and tired. Her breathing became rapid

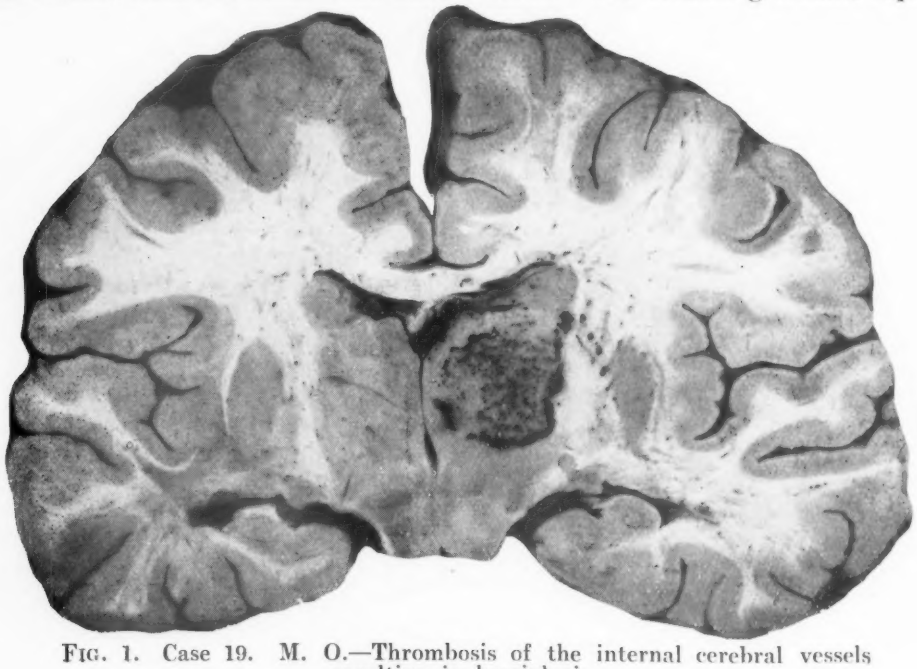

FIG. 1. Case 19. M. O.—Thrombosis of the internal cerebral vessels resulting in hemiplegia.

TABLE I.

Case.	Age and sex.	Etiology.	Clinical notes.	Pathological findings. Thrombosis	Pathological findings.
1 L.B.	2 years F.	Pneumonia	Developed empyema	Vessels over left cerebral hemisphere	Pneumonia and empyema
2 S.B.	16 months M.	Pneumonia	Pneumococcal meningitis	Sup. long. sinus Right lateral sinus Right cerebral vessels	Early meningitis (Pneumococcal)
3 H.J.	4 years M.	Sinusitis, sphenoid and ethmoid	Swelling of right eye	Right cavernous sinus Right ophthalmic vein Right (Sylvian fissure) cerebral veins	Extra-dural abscess Sphenoid and ethmoid sinusitis
4 A.K.	9 years F.	Sphenoid sinusitis	Bronchopneumonia	Both cavernous sinuses	Multiple lung abscesses
5 C.R.	12 years F.	Mastoiditis	Mastoidectomy Right jugular vein tied off	Right lateral sinus	Pneumonia Mastoiditis
6 S.D.	6 years F.	Mastoiditis	Mastoidectomy	Right lateral sinus	Subdural abscess
7 W.H.	4 years F.	Mastoiditis	Mastoidectomy	Left lateral sinus	Pneumonia
8 I.G.	8 years F.	—	Swelling of face	Cavernous (both) sinuses	Basal meningitis (Staphylococcus)
9 H.P.	4 years M.	Pulmonary tuberculosis	Enteritis	Sup. long. sinus	Miliary tuberculosis No evidence of meningitis
10 M.S.	9 months F.	Cervical abscess	Streptococcal meningitis	Right lateral sinus Purulent thrombus	Bilateral mastoiditis Streptococcal meningitis
11 D.J.	2 years F.	Pink disease Pneumonia	—	Right lateral sinus	Pneumonia

TABLE 1—*continued.*

Case.	Age and sex.	Etiology.	Clinical notes.	Pathological findings. Thrombosis.	
12 K.B.	13 months M.	Anaemia	Haemoglobin 29 per cent. Severe hypochromic anaemia	Sup. long. sinus Right lateral sinus Surface veins	Subarachnoid haemorrhage over right parietal region
13 T.B.	5 years. M.	Mastoiditis	Streptococcal meningitis	Cavernous sinus Lateral sinus	Ethmoid maxillary sinusitis Extension from mastoid
14 R.J.	11 months M.	Mastoiditis	Right otitis media	Sup. long. sinus Straight ? ? Both lateral sinuses Surface veins	Right mastoiditis No evidence of extension Renal infarcts
15 V.L.	3 months F.	Mastoiditis	Pneumonia	Both lateral sinuses	Mastoiditis
16 G.H.	17 months M.	Meningococcal meningitis	Pneumonia	Sup. longitudinal sinus Left lateral sinus Left cerebral veins	Left subarachnoid haemorrhage in parietal region
17 B.L.	7 months M.	Pink disease with pneumonia	Bilateral otitis media diarrhoea Transfusions of blood and 5 per cent. glucose given into anterior fontanelle	Sup. longitudinal sinus Middle cerebral vessels	Bilateral mastoiditis
18 E.R.	1 year M.	Otitis media 9 months	Developed pneumonia and empyema (pneumococcus)	Right lateral sinus	Pus in maxillary ethmoid, sphenoid and mastoid antra. Empyema and pneumonia
19 M.O.	2 years F.	? Tonsillitis	Sudden onset, restlessness, twitching	Sup. long. and lateral sinuses Ext. cerebral veins Int. cerebral veins	Only focus of infection was tonsil crypts (haem. strep.)
20 J.B.	16 months	Otitis and sinusitis	Sudden onset, restlessness, convulsions	Sup. long. sinus Cerebral veins	Subarachnoid haemorrhage (pneumococcus Type 1)
21 J.B.	2 years F.	Unknown	Sudden onset, drowsiness, fever, convulsions, purpura	All sinuses External jugular vein Choroid plexus Veins of Galen	Pus in both middle ears. (haem. strep.) Infarcts in lungs and kidneys.

22 S.W.	2½ years F.	?Mastoiditis	Sudden onset. No clinical evidence of site of infection	Cerebral veins left side Left choroid plexus	Pus in middle ear and mastoid antrum. (haem. strept.) Recent haemorrhagic infarct in upper pole rt. kidney.
23 S.S.	10 months M.	?Mastoid	Drowsiness, increasing three months	Sup. long. sinus Both lateral sinuses Cerebral veins	Pus in right middle ear and mastoid antrum. Bronchopneumonia.
24 I.H.	9 months M.	Mastoiditis. Post-basic meningitis	Hydrocephalus, fever and vomiting for ten weeks	Left lateral sinus	Chronic basal meningitis, Internal hydrocephalus. Left mastoiditis.
25 I.C.	7 months M.	Unknown	Sleeplessness and twitching of legs	Sup. long. sinus Both lateral sinuses Cerebral veins	Thin purulent material in both middle ears (haem. strept.).
26 S.P.	4½ months M.	Cervical abscess	Abscess opened and healing at onset of nervous symptoms	Sup. long. sinus Both lateral sinuses Cerebral veins	Pus in right middle ear (haem. strept.)
27 P.J.	8 months F.	Mastoid	Drowsiness Spastic legs	Sup. long. sinus Cerebral veins	Subarachnoid haemorrhage, upper part left Rolandic area.
28 R.C.	1 month M.	Pneumonia	Vomiting Cyanosis	Sup. long. sinus Cerebral veins	Thin purulent fluid in both middle ears and both maxillary antra.
29 C.S.	13 days M.	? Sepsis neonatorum	Impetigenous skin lesions Convulsions	All cerebral venous sinuses	Umbilical veins contained soft thrombus.
30 J.H.	5½ years F.	Cervical abscess	Acute nephritis Otitis media Abscess opened four weeks before death	Both lateral sinuses	Subacute nephritis Left mastoiditis Left maxillary sinusitis (haem. strept.)
31 N.E.	2 years M.	Cellulitis of orbit	Convulsions one hour after incision of conjunctiva. Death in twelve hours	Right cavernous sinus	
32 M.M.	26 days F.	Pneumonia	Drowsiness Terminal gastro enteritis	Sup. long. sinus Cerebral veins Lateral sinuses	Otitis media.

and she lapsed into unconsciousness in two or three hours. Twitching of the arms and legs was then noticed. She regained consciousness in a short time and vomited. Later in the day the child had a definite convulsion and remained unconscious after the seizure. The morning after the onset the right arm and leg were found to be weak. She was feverish from the onset and the temperature remained about 102° F. throughout. Convulsive twitchings of the right side of the body continued after admission to the hospital. A lumbar puncture revealed 1,000 creneated red blood cells per c.mm. with no increase of white blood cells. Cultures were sterile. A blood count showed 24,800 leucocytes with 81 per cent. polymorphonuclears and evidences of slight toxic changes. Twitching of the right arm and leg continued throughout the next four days. The fifth day after admission she seemed improved and took feeds well, but the following day she became drowsy and was very difficult to arouse. There was a slight stiffness of the neck, stertorous breathing and an irregular pulse. Spasticity of all her limbs developed. Her condition had rapidly become worse. A trephining operation was done over the left meningeal area because cerebral haemorrhage, tumour or abscess had to be considered in the differential diagnosis of a child who was becoming rapidly worse. At operation nothing was found beyond congestion and increased pressure. The following day the child could not swallow, there was marked general rigidity, and she died eleven days after the onset. A summary of the cerebro-spinal fluid findings is shown in the following table.

TABLE 2.

CEREBRO-SPINAL FLUID FINDINGS IN CASE 19.

DAY	LEUCOCYTES per c.mm.	RED BLOOD CELLS per c.mm.	SUGAR per cent.	CHLORIDES per cent.	PROTEIN per cent.
1	6	1,000	56 mgm.	876 mgm.	90 mgm.
2	18	1,500	—	—	—
5	5	Slightly xanthochromic	—	—	—
8	8	,,	—	932 mgm.	125 mgm.

Post-mortem examination revealed a terminal broncho-pneumonia of the lower lobes of both lungs. The brain was markedly congested; all of the superficial blood vessels were thrombosed, also the vessels in the substance of the brain, chiefly on the left side in the region of the thalamus and internal capsule. All of the venous sinuses were thrombosed (see figure 1). The only focus of infection was a purulent exudate in the crypts of both tonsils which were hypertrophied. Post-mortem blood cultures and cultures of the thrombus in the superior longitudinal sinus remained sterile.

Case 20. J. B., a girl, aged sixteen months was admitted with a history of having been well until the day before admission, when she appeared flushed, became very restless and the following morning developed convulsions, which continued after admission to the hospital. The convulsive twitchings were at first generalized, but later became confined to the left side of the face, the left arm and leg. A lumbar puncture relieved the convulsions. The cerebro-spinal fluid was clear, was under increased pressure and contained 4 cells per c.mm., no sugar, chlorides 774 mgm. per cent., protein 13 mgm. per cent. On examination there was no neck rigidity, Kernig's sign was negative and the reflexes were normal. There was no evidence of infection. A blood culture remained sterile. The child continued to be very restless, resented being touched, and at times seemed to be semi-conscious, although she could take fluids. The temperature was normal and remained so until the day before her death, when it became

elevated to 102° F. The day after admission the left arm and leg became paralyzed, the neck became stiff and the Kernig sign was positive on both sides. The reflexes were absent on the left side. During the next four days her condition became rapidly worse. In the late stages of her illness bluish-black areas appeared on the neck, hands, ears and nose due to thrombosis or emboli in the terminal vessels. A fine purpuric rash was present over the lower legs and a few purpuric spots on the backs of the hands.

The child died nine days after the onset. In view of the sudden onset with convulsions and meningeal signs without cerebro-spinal fluid findings of meningitis, and experience with the previous case, a diagnosis of cerebral sinus thrombosis was made. At post-mortem examination the brain showed a diffuse gelatinous haemorrhagic area in the region of both Rolandic areas and extending over the cortex. This was more marked on the right side. All of the superficial veins and the superior longitudinal sinus were thrombosed (see figures 2 and 3). Purulent exudate was found in both

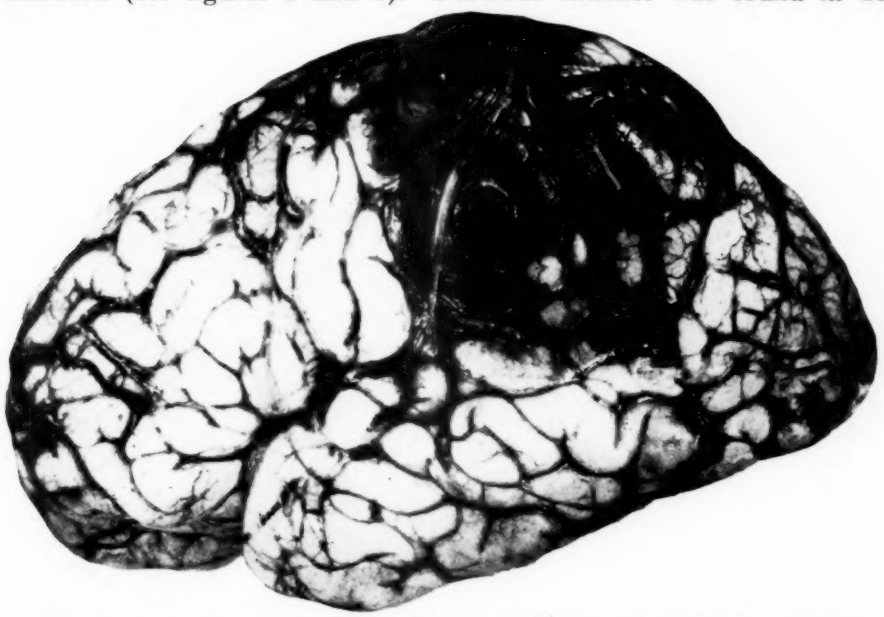

FIG. 2. Case 20. J. B.—Left cerebral hemisphere showing thrombosis superficial vessels and the associated subarachnoid haemorrhage.

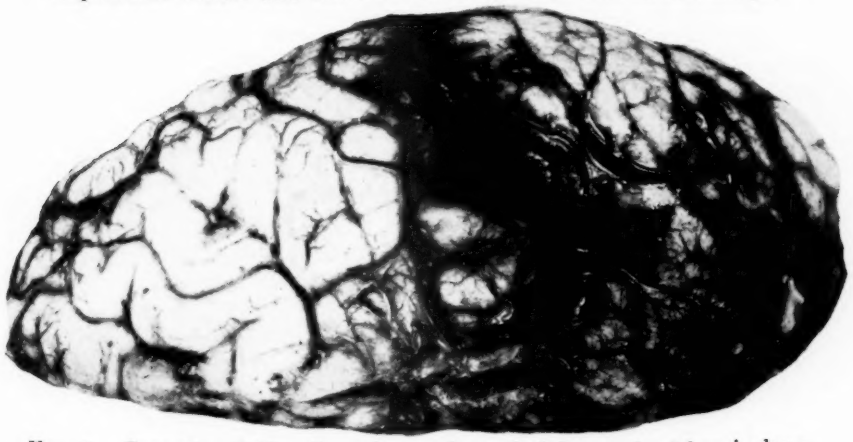

FIG. 3. Case 20. J. B.—Superior surface of right cerebral hemisphere.

maxillary antra, ethmoid cells, middle ears and mastoid antra. This pus was cultured and grew pneumococcus type 1, which was also cultured from the clot in the superior longitudinal sinus.

The above two cases were outstanding in their sudden onset without any evident infection during the course of illness. The cultures of pneumococcus in one case and the presence of a septic tonsillitis in the other are possible etiological factors.

Case 21. J. B., a girl, aged two years, was an only child of healthy parents, who was well until the day before admission, when she became feverish and was put to bed. At 3 a.m. she had a convulsion lasting about ten minutes, with frothing at the mouth, eyes rolled up and twitching of both arms and legs. At 6 a.m. she had a similar convulsion lasting twenty minutes which was followed by vomiting of brown frothy fluid and upper abdominal pain. She had not been in contact with any known infection. When examined upon admission to the hospital the child was rolling her head from side to side, but apart from this she showed no abnormal signs. The temperature was 105·4° F., pulse 160 and respirations 48. The temperature remained elevated between 102° and 103° F. for one week.

FIG. 4. Case 21. J. B.—Purpuric rash over right leg.

The only focus of infection was a mild pyelitis. The child vomited several times daily for the first week but only occasionally subsequently. Four days after admission the legs became hypertonic but there were no other signs of disturbance of the nervous system. It was later noted that the child appeared to be blind and she continually opened and closed her mouth. This was associated with clonic spasms of both upper limbs, the right arm and hand being more affected than the left. The legs were normal but a definite stiffness of the neck had developed. A lumbar puncture revealed 62 red blood cells per c.mm. and 6 white blood cells per c.mm. The cerebro-spinal fluid sugar was 48 mgm. per cent., the chlorides 766 mgm. per cent. and the protein 23 mgm. per cent. The spinal fluid and urine were searched for tubercle baccilli but none were found and the Mantoux test was negative. The blood urea was 23 mgm. per cent. and the non-protein nitrogen 21 mgm. per cent. A blood culture remained sterile during five days' incubation. Cultures of the cerebro-spinal fluid were also sterile. The blood showed 90 per cent. of haemoglobin with normal colour index. The leucocytes numbered 7,700 per c.mm. and the differential count showed 20 per cent. of segmented polymorphonuclear cells and 40 per cent. non-segmented forms. The Wassermann reaction was negative. An x-ray examination of the lungs showed no evidence of pneumonia or tuberculosis. A purpuric rash

developed four days before her death which first appeared in both groins and later over both legs (see figure 4). Twelve days after admission there was a slight purulent discharge from the right ear which did not recur. The legs gradually became more spastic and the head retracted. There were frequent twitchings of both hands with an increased rigidity of the arms. The left external jugular vein became very prominent and a thick firm thrombus could be palpated throughout its entire length. The child remained drowsy with long periods of semi-consciousness, a variable temperature and gradual decline in general health until she died six weeks after admission to the hospital.

At post-mortem examination the skin showed numerous purpuric spots over the legs, arms and trunk, but most marked on the legs (see figure 4). The lungs contained several embolic infarcts and haemorrhagic areas. Both

FIG. 5. Case 21. J. B.—Thrombosis of the superficial vessels and subarachnoid haemorrhage.

kidneys showed septic embolic infarcts. All of the venous sinuses of the skull were thrombosed. The thrombosis extended from the superior longitudinal sinus along the lateral sinuses and down into the jugular vein. The left external jugular vein was markedly distended and thrombosed throughout its complete length. The straight sinus, inferior saggital and veins of Galen were thrombosed. The majority of the large superficial veins showed thrombosis. There was considerable subarachnoid haemorrhage over the left occipital lobe, another over the right midparietal region and a small one over the superior surface of the right frontal lobe (see figure 5). The vessels in the left choroid plexus were completely thrombosed as were the vessels in the surrounding brain substance. There was considerable

softening of the brain in this area (see figure 6). There was thick yellow pus present in both middle ears and mastoid antra, from which a pure culture of a haemolytic streptococcus was grown.

The outstanding feature of this case was an illness of six weeks' duration without any evidence of infection except pyelitis. Whereas at post-mortem examination the mastoids were found to be grossly infected with pus which grew a haemolytic streptococcus.

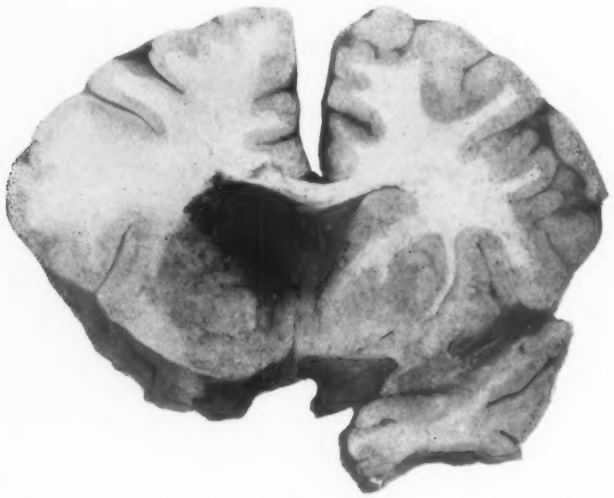

FIG. 6. Case 21. J. B.—Thrombosis of choroid plexus.

Case 22. S. W., a girl, aged two-and-a-half years, was well until four days before admission, when she became tired in the afternoon and slept for a long time. It was then noticed that she could not use her right hand and could not speak. The following day the right hand and the right side of the face showed marked twitching which continued until the day before admission. The right leg was then noticed to be motionless. The child was restless between long periods of drowsiness. In the hospital she gradually became more comatose. The temperature ranged between 100° and 104° F. The right ear drum was pale but not bulging. There was neck rigidity and a positive Kernig sign. The right side of the face showed some weakness and the right arm was completely paralyzed and flaccid. The right leg became spastic and when touched it would go into a clonic spasm. The left side appeared normal until a few hours before death when the left hand began to twitch. The cerebro-spinal fluid contained 8 leucocytes and 17 red blood cells per c.mm. The cultures were sterile. Biochemical examination revealed sugar 70 mgm. per cent., chlorides 866 mgm. per cent. and protein 10 mgm. per cent. The plasma chlorides on the same day were 695 mgm. per cent. A throat swab grew chiefly a haemolytic streptococcus. A blood count showed haemoglobin 104 per cent., erythrocytes 5,600,000 per c.mm., leucocytes 11,200 per c.mm. and the differential count was as follows: Polymorphonuclears 58 per cent. (30 per cent. non-segmented, 28 per cent. segmented), metamyelocytes 2 per cent., lymphocytes 36 per cent. and monocytes 4 per cent. The urine examination showed the following:—albumin – cloud; sugar – none; acetone + +;

deposit – hyaline casts, occasional red blood cells, pus cells 2 or 3 per H.P.F. and a very occasional granular cast.

Post-mortem examination revealed a well-nourished child with a haemorrhagic infarct in the upper pole of the right kidney with an area of softening surrounding it. The cerebral venous sinuses showed no evidence of thrombosis. There was some thrombosis of the branches of the Sylvian vein and the vessels over the left parietal region. The sulci in this region showed thrombosis of the vessels on the suface of the cortex with slight subarachnoid haemorrhage and a haemorrhagic necrosis in the surrounding brain tissue. The other vessels of the brain were engorged, but no other thromboses were found. There was pus in the right middle ear and mastoid antrum which was cultured and grew a haemolytic streptococcus.

The above four cases have each shown an unusually high level of chloride in the cerebro-spinal fluid. A summary of the cerebro-spinal fluid findings is given in table 3.

Case 23. S. S., a boy, aged ten months, had been a normal breast-fed infant until three months before admission, when he began to sleep for lengthening periods until finally he could be aroused only with difficulty. He developed a cough and bronchitis three weeks before admission to the hospital. Examination revealed a well-developed and well-nourished pale infant with irregular respirations. He was listless and drowsy, and disinterested in his surroundings. The eyes following a bright light and the pupils reacted slowly. The discs were normal. There was a slight stiffness of the neck. The limbs moved occasionally with stimulation but they appeared weak, the legs being weaker than the arms. Muscle tone was decreased and the reflexes were absent. Plantar response was extensor and the Kernig sign negative. There was twitching of both arms and legs for a short time after admission to the hospital. A lumbar puncture was performed and clear cerebro-spinal fluid was withdrawn under no increase of pressure. The cell count was 3 leucocytes per c.mm. The chemical analysis revealed—sugar 25 mgm. per cent., chlorides 680 mgm. per cent. and protein 13 mgm. per cent. In view of these findings further spinal punctures were not performed. The fatty acid, cholesterol and phospholipoid estimations in the blood were within normal limits. The serum calcium was 9·8 mgm. per cent. Four days after admission the child developed a temperature of 104° F. which subsided to 100° and 101° F., and was associated with a right otitis media which did not appear severe. The child's mental condition appeared to improve at times when he would take his feeds better and occasionally be interested in his surroundings. A blood count showed:—Haemoglobin 62 per cent., erythrocytes 3,500,000 per c.mm., leucocytes 3,800 per c.mm. Differential—Neutrophil polymorphonuclears, segmented, 12 per cent.; neutrophil polymorphonuclears, non-segmented, 12 per cent.; eosinophil polymorphonuclears, segmented, 1 per cent.; lymphocytes, large, 46 per cent.; lymphocytes, small, 23 per cent.; lymphocytes, immature, 2 per cent.; monocytes 4 per cent. Two normoblasts were found in counting 100 leucocytes. There was some anisocytisis.

At post-mortem examination a terminal bronchopneumonia was found in both lower lobes. On opening the skull the dura mater was found to be thickened and adherent to the bone. The convolutions of the brain appeared shrunken and the sulci very prominent. All of the superficial vessels appeared to be distended and thrombosed. There was an excess of cerebro-spinal fluid over the surface. All of the cranial venous sinuses contained an old-standing thrombosis (fig. 7). The accessory nasal sinuses were all found to be healthy, and also the left middle ear and mastoid

antrum. The right middle ear and mastoid antrum and cells contained thick pus, which grew a haemolytic streptococcus. Cultures of the thrombus were sterile.

The possibility of some previous meningeal irritation which would account for the lethargy and drowsiness for three months could not be ruled out in this case. The more reasonable explanation, however, would appear to be a partial thrombosis from the onset, possibly due to a respiratory infection which was not recognized by the parents.

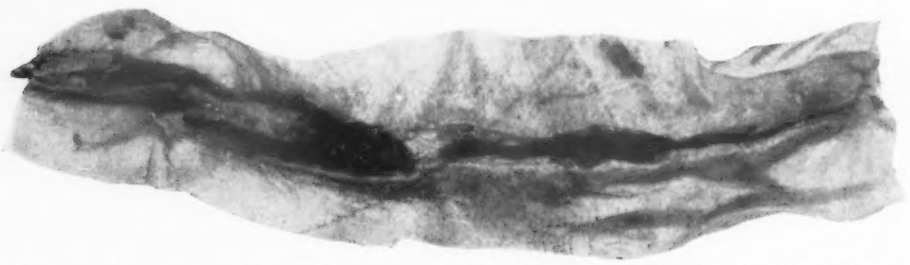

FIG. 7. Case 23. S. S.—Thrombus lying in exposed superior longitudinal sinus.

Case 24. I. H., a boy, aged nine months, suffered with post-basal meningitis for about six weeks before his admission to the hospital. The head became hydrocephalic with some retraction. The cerebro-spinal fluid contained 330 cells per c.mm., sugar nil, chlorides 617 mgm. per cent. and protein 127 mgm. per cent.

At post-mortem examination a chronic basal meningitis with marked internal hydrocephalus was found. The left lateral sinus was partially thrombosed as a result of an acute mastoid infection on that side.

This case illustrates the changes which are found in the cerebro-spinal fluid due to the original disease, in this case meningitis. Here the thrombosis of the lateral sinus was of recent origin and probably resulted from an acute mastoid infection. There were not any clinical signs which would suggest the presence of sinus thrombosis.

Case 25. I. C., a boy, aged seven months, was a normal infant who became sleepless and developed uncontrolled movements of the legs and tongue. He was found to have an external strabismus, slight neck rigidity and a positive Kernig sign on each side. The limbs were hypertonic and the reflexes brisk. Chvostek's and Trousseau's signs were negative. The child developed a convulsion in which the limbs were extended, the face was distorted and there was marked cyanosis. Later the right arm and shoulder was noted to be twitching. A lumbar puncture was performed daily for three days, the first one showed only a few red blood cells. The third specimen contained 12 leucocytes per c.mm., sugar 54 mgm. per cent., chlorides 696 mgm. per cent. and protein 40 mgm. per cent. The child's condition was variable, at times approaching normal, but usually extremely restless. Finally the head became retracted, vomiting forceful, both legs rigid, the head bathed in perspiration and the child screamed continuously unless under the influence of sedative. He finally died four weeks after his admission to the hospital and five weeks after the onset.

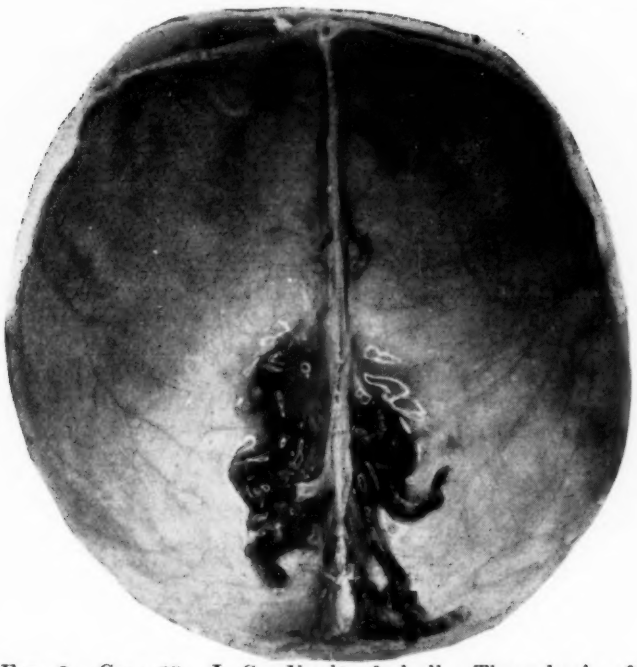

FIG. 8. Case 25. I. C.—Vault of skull. Thrombosis of the veins draining into the superior logitudinal sinus.

FIG. 9. Case 25. I. C.—Thrombus in exposed lateral sinus.

At post-mortem examination the vessels over the surface of the brain showed an extensive thrombosis. All of the cerebral venous sinuses showed some thrombosis, which extended along the lateral sinuses and into the right jugular foramen (fig. 8 and 9). Both middle ears contained a moderate amount of thin purulent material. Cultures of this material grew an haemolytic streptococcus and haemolytic staphylococcus albus.

Case 27. P. J., a girl, aged eight months, was a well-developed and well-nourished infant, perfectly well until one week before being sent to hospital, when she became drowsy and vomited occasionally. Later she became very restless and pallor was noticed. The legs twitched occasionally and finally became stiff. Examination revealed a positive Kernig sign on both sides and the neck was rigid. The knee jerks were present and equal. Pus cells and albumin were found in the urine. The cerebro-spinal fluid contained 35 leucocytes per c.mm. and 62 red blood cells per c.mm. A differential count of the leucocytes showed 60 per cent. polymorphonuclears and 40 per cent. mononuclears. Cultures were sterile. A blood count revealed a hypochromic anaemia:—Haemoglobin 45 per cent., red blood cells 3,520,000 per c.mm., colour index 0·64 and leucocytes 19,000 per c.mm. After showing an irregular, septic temperature for four days the child died with generalized convulsions and cyanosis. At post-mortem examination the superior longitudinal sinus and the cerebral vessels draining into it showed an extensive thrombosis (fig. 10). There was an area of sub-

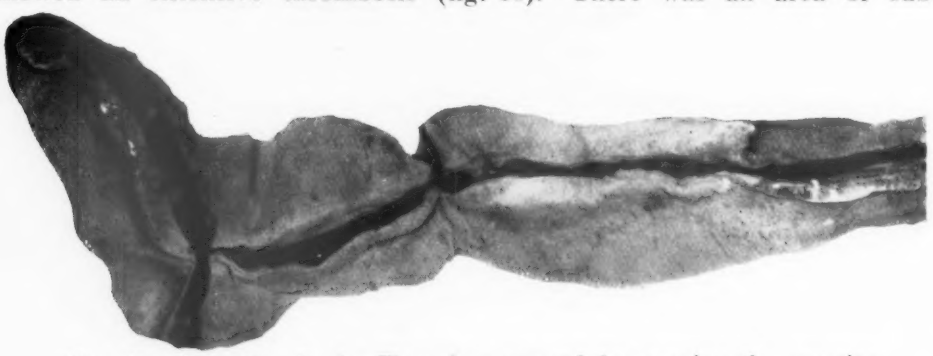

FIG. 10. Case 27. P. J.—Thrombus exposed by opening the superior longitudinal sinus.

arachnoid haemorrhage over the upper part of the left Rolandic area. Both middle ears and the mastoid antra contained thick creamy pus. The kidneys showed several pyaemic abscesses. Cultures of material from the ears grew H. influenzae and pus from the kidney grew B. coli.

Symptomatology

A study of the eight cases which have been summarized reveals a number of common signs which have assisted in arriving at a proper diagnosis. The usual history obtained is one of a previously healthy child who suddenly becomes drowsy or tired with periods of extreme restlessness followed by convulsions or localized twitchings of some part of the body. The story then goes on to paresis of limbs, face, tongue or eye muscles and sometimes marked spasticity. Rhythmic movements and clonic spasms were frequent and vomiting and feverishness were complained of in several instances. A stiff neck, with or without head retraction, a positive Kernig sign and absent reflexes were usual findings. A marked purpuric rash developed,

chiefly over the skin of the extremities in three children. A not uncommon observation was irregular breathing and irregular pulse. The variability of the mental state and periods of semi-consciousness or unconsciousness were sometimes outstanding features. The temperature was extremely variable. Thus in case 19 the temperature remained at 102° F. throughout the illness, whilst in case 20 it remained normal or subnormal except on two readings when it reached 100° F. The former showed far less evidence of infection post mortem than the latter. Case 27 ran a swinging, high temperature throughout, which was explained by the findings at autopsy of pyogenic abscesses in the kidneys and gross infection of the mastoids and sinuses. All patients developed some elevation of temperature during the course of the illness, but this was often intermittent.

The above signs and symptoms are by no means confined to cerebral sinus thrombosis, nor do they occur in every patient. However, they occurred sufficiently often in this small series of cases that the condition was usually considered in the differential diagnosis. Those cases associated with direct extension from a mastoiditis to the lateral sinus, or of infection of the face into the cavernous sinus, usually present a group of symptoms which are more easily recognized and which are described in standard text-books. These sinuses are not connected directly with the vessels which drain the brain, and therefore if they become blocked there are alternative routes for the return flow of blood, and severe cerebral symptoms do not usually occur. Thrombosis associated with meningitis is usually marked by the primary disease. The other cases form a group which show the foregoing signs and symptoms sufficiently often to produce a syndrome which should be considered in the differential diagnosis of cerebral conditions in children.

Differential diagnosis

The other cerebral conditions which give rise to signs and symptoms resembling sinus thrombosis are meningitis, cerebral abscess, cerebral haemorrhage, cerebral tumour and encephalitis. The most difficult of these to rule out in the diagnosis of cerebral sinus thrombosis is often cerebral haemorrhage, since there is some haemorrhage usually present with thrombosis. However, the amount of haemorrhage and therefore the number of red blood cells per c.mm. is usually much less in sinus thrombosis than in cerebral haemorrhage. The signs and symptoms are more constant with haemorrhage and usually more sudden in onset. Purulent meningitis is usually easily differentiated from sinus thrombosis, but tuberculous and post-basal meningitis present some similar findings. In purulent meningitis the fluid contains large numbers of polymorphonuclear cells. In all forms of meningitis the sugar content is reduced or absent; the chlorides are lowered, this being most marked in tuberculous meningitis; the protein is higher than in sinus thrombosis. Cerebral abscess and cerebral tumour lead to papilloedema much more frequently than thrombosis, and their onset is much slower. The clinical picture of sinus thrombosis is much more

acute than the gradual procession of signs and symptoms in abscess and tumour. The cerebro-spinal fluid is usually unaltered in the two latter conditions. Occasionally the cell count may be slightly increased in brain abscess, but here the presence of red blood cells, xanthochromic fluid, or increased chlorides may help in making a diagnosis of sinus thrombosis. The absence of polymorphonuclear leucocytes in the cerebro-spinal fluid in encephalitis is a differential point, but the signs and symptoms are often similar to sinus thrombosis. Experimental work recently reported by Frenckner[9] suggests a possible diagnostic aid by the use of x-rays and the injection of x-ray opaque substance into the superior longitudinal sinus. This method shows the point at which the thrombus causes obstruction, and in some cases might lead to successful operative interference. At present the prognosis is hopeless in the majority of cases unless the thrombosis is confined to the lateral sinus.

The cerebro-spinal fluid

Patients suffering from thrombosis of cerebral vessels usually present signs and symptoms which indicate a severe intracranial lesion and therefore a lumbar puncture becomes almost essential in making an accurate differential diagnosis. Reference to table 3 brings out several points in the

TABLE 3.

	Leucocytes	Red blood cells	Sugar	Chlorides	Protein
	per c.mm.	per c.mm.	mgm. per cent.	mgm. per cent.	mgm. per cent.
Case 19 (1)	6	1,000	56	876	90
(2)	8	Xanthochromic	—	932	125
Case 20	4	0	0	774	13
Case 21	6	62	48	766	23
Case 22	8	17	70	866	10
Case 23	3	0	25	680	13
Case 24	330	0	0	617	127
Case 25 (1)	4	90	—	—	—
(2)	6	Slight blood tinge	—	—	—
(3)	20	1,950	54	696	40
Case 27	35	62	—	—	—

examination of the cerebro-spinal fluid which are of considerable importance in arriving at a diagnosis of cerebral thrombosis. The leucocytes are usually within normal limits but occasionally may be slightly raised. (In case 24 the increase to 330 per c.mm. was a result of the meningitis.) A differential

count of the leucocytes usually shows a preponderance of polymorphonuclears. Red blood cells may, or may not be present. The number of these varied from 17 to 1,950 per c.mm. in five out of the eight cases in which the fluid was examined. The presence of red blood cells, excluding traumatic haemorrhage of course, is practically always due to some degree of subarachnoid haemorrhage in the region of the thrombosed vessels. This was true in all of the cases in table 3 which showed red blood cells in the cerebro-spinal fluid, while the others with an absence of red blood cells showed no evidence of subarachnoid haemorrhage.

Greenfield and Carmichael[11] state that every case of cerebral thrombosis is associated with some haemorrhage from capillaries and that this accounts for the few red blood cells and the not uncommon finding of xanthochromic fluid. Ehlers and Courville[3] emphasize the importance of a bloody or xanthochromic fluid in the diagnosis.

The chemical changes in the cerebro-spinal fluid were particularly interesting. The amount of sugar present varied from normal to a complete absence and in the presence of meningitis the sugar was lowered or completely absent. Unless complicated by meningitis the cerebro-spinal fluid proteins were within normal limits or slightly raised, the values tending to be higher in those specimens which contained red blood cells. There is usually no record of the chloride content of the spinal fluid in the cases which have been reported in the literature. It will be seen that the majority of the cases in this series in which estimations were made on the cerebro-spinal fluid the chlorides reached a high level. This occurred sufficiently often to make it almost diagnositic. In four cases the high value for chloride suggested the possibility of cerebral sinus thrombosis. Figures of 876, 932 and 866 mgm. per cent. are strikingly high and have not been encountered in other conditions in children. An analysis of one thousand cerebro-spinal fluid chloride estimations carried out in this hospital reveals no figures as high as these. Neale and Esslemont[12] working in this hospital found the chloride values in non-meningitic cases varied from 696 mgm. per cent. to 783 mgm. per cent. with average of 730 mgm. per cent. Greenfield and Carmichael[11] give the normal range of cerebro-spinal fluid chlorides as 720 to 740 mgm. per cent., and state that a chloride value above 750 indicates renal deficiency with impermeability to chlorides. A histological study of the kidneys in these cases of cerebral sinus thrombosis has not revealed any changes which might explain an impermeability to chlorides. Whilst Neale and Esslemont[12] showed that the amount of chloride in the cerebro-spinal fluid varies to some degree with that in the blood, the administration of sodium chloride solutions intravenously, or by other routes, will not explain the high figures, since only two of the patients received rectal saline. Blacklock and Morris[13] have recently reported interesting work on experimental chloride retention in rabbits. They have shown that there is a retention of chloride in heart, liver, brain and skeletal muscle in the presence of acute infection. The possibility of this retention being due to the kidneys becoming less permeable to chloride is, in their opinion, difficult to believe

because the kidney has not lost its ability to concentrate and excrete urea and other substances. This seems to be borne out in case 21, whose blood fortunately was examined at the same time as the cerebro-spinal fluid. The cerebro-spinal fluid chlorides were 766 mgm. per cent., while the blood urea was 23 mgm. per cent. and the non-protein nitrogen 21 mgm. per cent.

Causation of thrombosis

Byers and Hass[5] have reviewed many possible etiological factors in the mechanism of thrombosis, such as the severe loss of fluids in diarrhoea and vomiting and the associated polycythemia in some cases. The administration of blood and other fluids has been suspected as a possible cause of thrombosis, but the above authors found that not all of their patients had received such treatment, nor could they find evidence of destruction of the endothelial lining by bacteria or toxins. Simpson[7] felt that intravenous therapy via the anterior fontanelle into the superior longitudinal sinus played a large part in the formation of thrombosis in some of his cases. Case 17 in this series received a blood transfusion by this route, but the others had not received any intravenous therapy which could be of etiological significance. Ashchoff[10] speaks of the relation of the blood flow to the formation of thrombi, and slowing of the blood from various causes is favoured by Byers and Hass[5] as the most important etiological cause.

Although there was not an opportunity to carry out any special studies in the present series of cases, in view of the above theories several facts seem to be of importance. In the first place, none of the children had suffered any appreciable loss of body fluids before the signs of thrombosis were well established. None was associated with diarrhoea although in a few instances occasional vomiting occurred in the early stages of the illness. Intravenous therapy had not been used in any of the cases and thrombosis has never been found at post-mortem examination on several hundred patients who have received intravenous therapy. The extremely sudden onset of symptoms in the majority of these cases pointed to the early establishment of a thrombus and does not fit in with any theory of dehydration or stagnation of blood in the sinuses. Every patient showed evidence of some septic process at post mortem, even though it was not demonstrable during life, and this appears to be the only common factor. Why such infections should produce changes in sinus wall, which cannot be demonstrated, but which give rise to thrombosis, is difficult to explain, especially when it is considered that in a high proportion of children infection in some part of the body and usually in the middle ears is found at autopsy. It is recognized that convulsions are not uncommon during this age period in association with infections sometimes of a trivial nature; and it is conceivable that convulsions might have preceded the thrombosis in some of these cases, possibly producing conditions favourable to thrombus formation in the sinuses. Thrombosis is occasionally attributed to anaemia. An anaemia was present in only three of the cases recorded here, the haemoglobin values being 45, 62 and 29 per cent., and its importance is difficult to assess in comparison to the presence of infection.

A study of table 4 shows the possible etiological factors in this series of cases. Case 12 was the only one which did not have a demonstrable focus of infection, the only known factor here being a moderately severe nutritional anaemia.

TABLE 4.

Possible etiological factors in 32 cases.

Primary ear infection	9
Ear infection found p.m.	9
Accessory nasal sinus infection	6
Purulent infection elsewhere	7
Pneumonia	7
Anaemia	3
Terminal diarrhoea	2
Pulmonary tuberculosis	1

The conclusion to be drawn from these cases is that infection is probably the chief factor in the production of thrombosis, since, although it may not be detectable during life, it is nevertheless practically always found at autopsy. Toxins may be conveyed by the blood stream, producing an effect upon the vessels which leads to thrombosis.

Summary

Cerebral sinus thrombosis, although comparatively rare, appears to be increasing. Eight case summaries are reported with important facts relating to thirty-two cases recorded during fourteen years. A review of the principle signs and symptoms in these cases suggests that there is a fairly constant clinical syndrome associated with the majority of those cases which are not due to mastoiditis and cellulitis with involvement of the lateral and cavernous sinuses, respectively. There are in this group the following points which often assist in making a correct clinical diagnosis of sinus thrombosis:—Sudden onset of restlessness followed by convulsions; localization of the convulsions as shown by twitching and followed by paresis; cerebro-spinal fluid findings of increased or normal pressure, cells normal or slightly increased, the presence of red blood cells or xanthochromic fluid, cultures sterile, low sugar content, high chlorides and normal or slightly raised protein. The other points in the condition are the drowsiness and semi-consciousness; the rapid decline of general health in a previously healthy child, the post-mortem findings of thrombosis of cerebral vessels and in some cases the absence of any evident infection during the course of the illness. There is practically always an infection found at post mortem. The presence of high chloride values in the cerebro-spinal fluid is emphasized as an aid in arriving at the diagnosis. Several theories have been reviewed which attempt to explain the cause of the thrombosis, but no reference has been made to treatment or detailed pathology.

Thanks are due to the Honorary Physicians of the Children's Hospital for permission to use their case records.

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CONGENITAL OBLITERATION OF THE BILE DUCTS

IN A CHILD WHO LIVED FOR THREE YEARS AND THREE MONTHS

BY

CONSTANCE FINLAYSON, M.B., B.S.,
Adelaide.

The condition is comparatively rare although over 175 reports of cases have been recorded and reviewed by J. Thomson[1], Rolleston and Hayne[2], Parsons and Hickmann[3], Wyard[4], Hill[5], and others. The degree of severity of the lesions varies greatly. There may be blocking of patent ducts by inspissated bile giving rise to jaundice. Cases of this nature operated on by Ladd[6] cannot come into the category of obliteration of the bile ducts. In most instances death takes place in the first few months of life. Thomson says, ' If these children are not carried off by haemorrhage or some other such cause during the first week or two they generally live from three to eight months.' This case is reported because the child lived for over three years.

Case report

H. L., female, was born at Peterborough, South Australia, weighing 4½ lbs. The mother, aged 32 years, was a primipara. She appeared to be quite healthy and there was no history of miscarriages. Five weeks before full term there was bleeding from the uterus and a lateral placenta praevia was suspected but not felt. After twenty-four hours of moderate bleeding labour began spontaneously and after six hours the infant was born. The puerperium was normal except that the breast milk failed owing to the inability of the infant to suck.

During the first week the baby showed signs of slight jaundice, the colour deepening after the third week. She was at first fed on breast milk supplemented by a cow's milk and water mixture, then on cow's milk and water only, and as the gain in weight did not average more than three ounces a week various artificial foods were tried without avail. On April 10, 1933, the probable diagnosis was made of congenital obliteration of the bile ducts. At this time the jaundice was of a yellow green colour. The stools showed no bile pigment, the urine was deeply coloured. The weight was 8 lb. 14 oz. The Wassermann reaction was negative.

The child was first seen on September 26, 1933, at the age of ten months, and weighing 12 lb. 4 oz. The skin and sclerotics were a deep yellowish-green colour, the stools were pale and had been so from birth. The urine contained bile but otherwise showed no abnormality. The liver edge could be felt a finger's breadth below the right costal margin; the spleen was palpable. Signs of rickets were obvious, there was beading of the ribs and bowing of the long bones, especially the tibiae. Radiological examination of the bones showed the signs characteristic of the disease. The diet up to this period had consisted of a skimmed dried milk and baked flour. Radiostoleum was given in the first week of October, 1933, and the dose gradually increased from 5 minims to 30 minims daily. This was

continued until May, 1935, when the amount was reduced to 10 minims daily. The diet was increased to approximately that of a normal baby of ten months old except that fats, which tended to cause vomiting, were not given. The weight remained stationary for three weeks.

Laparotomy was suggested in the hope that the condition might prove amenable to surgical treatment. On October 18, 1933, under ether anaesthesia Dr. A. M. Cudmore opened the abdomen and explored the region of the gall bladder and bile ducts which were found in their usual anatomical position. The gall bladder was small, white in colour, with thick walls and appeared to be empty. No fluid, either bile or mucus, could be drawn into a hypodermic needle and syringe. The ducts were white in colour and felt like hard cords. It was obvious that no operative procedure could remedy the condition. Recovery from the operation was uneventful except for a fairly severe haemorrhage from the wound on the second day. The patient remained in hospital until December 8, 1933. Her diet at this time consisted of thirty ounces of skimmed milk, cereals, banana, scraped apple, spinach, brains, orange juice and 30 minims of radiostoleum daily. Her weight was now 13 lb. 4 oz.

The child was next seen on June 5, 1934. Jaundice was now deep green, the urine contained bile, the stools were clay-coloured. She now weighed 16 lb. 3 oz. The liver and spleen had increased in size. The signs of rickets were less. Pruritus was now a distressing symptom and had been present since January, 1934. She was continually scratching first one part of her body and then another, including her head. Scratch marks showed signs of bleeding especially behind the ears. There were raised circular areas in the skin slightly paler in colour than the body generally, arranged in clusters in regions that were most subject to scratching. These nodules appeared in March, 1934, two months after the pruritus began. In January, 1935, dextrose was suggested as a possible relief from the irritation. This was given in increasing amounts, beginning with three heaped teaspoonsful of the powder a day, until eight teaspoonsful were given as a routine in addition to the ordinary sugar in her food.

The patient was again seen in April, 1935. Her condition was as before except that the liver and spleen had increased in size and since taking the dextrose pruritus was much less troublesome. There were no obvious signs of rickets. During this visit to town she had a respiratory infection which lasted a few days, the temperature reaching a maximum of 102° F.

Writing in May, 1935, the mother states ' Since taking the dextrose in large quantities the irritation is wonderfully improved. The nodules in the skin seem very much flatter and quite a number have disappeared. I think I can correctly say that no fresh ones have appeared . . . Baby sleeps wonderfully well and is happy, the dextrose has made a wonderful difference to her night's rest. She walks quite well.'

The child was seen on February 25, 1936, aged three years and three months and weighing $22\frac{3}{4}$ lb. with a height of $33\frac{1}{2}$ inches. The jaundice was now of a blackish green hue. The liver was greatly enlarged, the lower edge being felt a hand's breadth below the right costal margin on a level with the umbilicus. The spleen was palpable as an elongated hard mass filling the left half of the abdominal cavity with its lower pole in the left iliac fossa. The teeth were badly decayed, the upper incisors had broken off level with the gum margin. The cutaneous nodules had disappeared except for a few flattened ones in the groins, axillae and in the bend of the elbows. No pruritus was present; she walked, talked and seemed happy (fig. 1). The haemoglobin was 45 per cent. (Sahli).

On March 2, 1936, the child became listless, refused food and appeared to have a slightly sore throat. Respiration was rapid and the temperature 104·8° F. There were no abnormal signs in the chest. Next day she was

drowsy and cried out at intervals. The abdomen became distended, the urine contained bile and pus cells were present microscopically. There was no reduction of Fehling's solution. The right eyelid and periorbital region became swollen owing to a subcutaneous haemorrhage.

On March 5 there was slight haemorrhage from the mucous membrane of the mouth. The child's condition became rapidly worse and death took place at midday.

FIG. 1.

I am indebted to Dr. E. McLaughlin for the following report on a blood film:—

> The erythrocytes show anisocytosis, some pallor, poikilocytosis and polychromatophilia. No nucleated forms seen. A very occasional myelocyte seen, otherwise there appears to be no very definite disturbance of the leucocytes. Abundant platelets present. The anaemia is of the hypochromic type.

Post-mortem findings. Professor J. B. Cleland kindly supplied the following notes:—

> The body was deeply jaundiced with very little subcutaneous fat and no excess of fluid in the peritoneal cavity. There were a few adhesions in the region of the gall bladder. The gall bladder was small, 3 cm. × 1 cm. in size. Its contents were bile-stained. From the neck of the gall bladder a duct was pervious and bile-stained for half an inch, after which it was represented by an apparently impervious cord the size of thick catgut, extending straight downwards towards the ampulla of Vater and not showing any branches or connexion representing a junction with hepatic ducts. A probe could with difficulty be inserted into the ampulla of Vater from the lumen of the duodenum. The liver was tough and its substance very firm with a smooth capsule and was mottled olive-green in colour. The glands in the hilum of the liver were not enlarged although the mesenteric glands seemed rather red and slightly bigger than normal. The pancreas seemed normal. The spleen, which

weighed 18½ ounces, was very large and extended to the iliac fossa; it was fairly firm, dark red in colour, and the Malpighian bodies were not recognizable. In the left kidney were groups of small abscesses with surrounding congestion at the upper pole, extending nearly to the pelvis. The right kidney showed two or three small white abscesses surrounded by red rings. Both kidneys were deeply jaundiced. The suprarenal glands were dark in colour and seemed to lack lipoid. There were numerous haemorrhages in the lungs with deep bile staining. In the skin on the upper part of the thigh and the abdominal side of the groin were little elevations about 1 mm. in size, suggesting xanthomata. Microscopic examination of the liver showed a considerable amount of fibrosis, in some places unilobular and in other places intralobular; there were a number of lymphocytes in parts; there were occasional clumps of inspissated bile between the liver cells but no obvious distension of bile ducts. In the spleen the pulp was filled with red cells and an occasional plasma cell was seen. In the pancreas the islands were very large and often there were several close together. There were abscess cavities in the kidneys with cloudy swelling. Sections of a lymph gland showed prominence of the reticulo-endothelium and the presence of old blood pigment. The lung showed some alveoli packed with red cells and in others a grandular exudate. Sections of the elevation of the skin showed a few foamy cells beneath the epithelium. Staphylococcus aureus was grown from the kidney.

Dr. W. R. Morris, of Peterborough, kindly supplied the notes on the antenatal and early postnatal history.

Summary

This case is reported for the following reasons:—

1. The duration of life. As this condition is incompatible with life it is surprising that this child reached the age of three years and three months. The majority of cases reported in the literature have died before the eighth month. Patients who have lived longer than the one now reported have been proved to have had partial obstruction of the common duct with intermittent jaundice.

2. The absorption of vitamin D. It would seem that vitamin D present in radiostoleum is capable of being absorbed in the absence of bile in the intestine, as shown by the cure of rickets. One recorded case showed that the administration of cod-liver oil failed to arrest the development of rickets.

3. Relief of pruritus. This distressing symptom was relieved by giving eight teaspoonsful of dextrose daily in addition to the usual sugar and starch of the diet.

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AN INVESTIGATION INTO THE HEALTH OF 1,530 PRE-SCHOOL CHILDREN

BY

PETER HENDERSON, M.D. (ABERDEEN), D.P.H.,
Deputy Medical Officer of Health, Leyton,
Late Assistant Medical Officer of Health, St. Helens.

It is a recognized and unpleasant fact that approximately 16 per cent. of the entrants to the elementary schools of this country possess physical defects that require treatment[1]. Less clearly known are the age at which these defects first appear in the child's life and the factors giving rise to them. It was in an attempt to obtain this information that the investigation now to be described was made. During the period January–July, 1936 (inclusive), 1,530 pre-school children were examined at five Infant Welfare Centres in the Borough of St. Helens. It was found that, of the 1,014 children under two years of age, 526 (51 per cent.) had physical defects other than constipation and disorders due to faulty methods of feeding; and of the 516 children over the age of two years 362 (70 per cent.) had one or more bodily defects. The defects found, with the number in each age-group, are given in table 1. It is proposed here to deal only with the defects number 1–15 in this table as it is thought that the defects number 16–29, though certainly important, need no further comment.

1. Digestive disorders

(a) **Due to faulty feeding.** 104 infants were affected. 'Wind' and 'green stools' were most frequently complained of by the mother. More infants suffered from over-feeding and too frequent feeding than from under-feeding; and bottle-fed babies gave the most trouble. Careful investigation into the quality and quantity of the feeds and into the technique of feeding, with the utilization of 'test feeds' for breast-fed babies that failed to thrive, usually made it possible to set the infant on the right road within a reasonably short time. Only a few cases merited admission to hospital. True cases of summer diarrhoea were rarely seen. The practice of giving excess sugar to infants was found to be prevalent and hard to stop. In 192 cases this practice was admitted. It is interesting to note that of the

TABLE 1.

No.		Age Groups	0–1	1–2	2–3	3–4	4–5	Totals
		No. of Children in each Age Group	652	362	193	212	111	1530
1	Digestive Disorders.	(a) Disorders due to faulty feeding	104	—	—	—	—	104
		(b) Constipation	50	26	3	2	2	83
2	Congenital Heart Disease		4	—	2	2	1	9
3	Skin Diseases.	(a) Seborrhoea Capitis ...	46	—	—	—	—	46
		(b) Others	36	30	18	8	7	99
4	Hernia.	(a) Umbilical	50	2	—	—	—	52
		(b) Inguinal	2	2	1	—	—	5
5	Orthopaedic Defects.	(a) Talipes	6	—	1	—	1	8
		(b) Severe Flat Foot, Knock-Knee, etc.	—	3	12	9	4	28
6	Defects of the Nervous System.	(a) Epilepsy	—	—	—	2	—	2
		(b) Severe Convulsions ...	4	—	—	—	—	4
		(c) Meningocele	—	—	1	—	—	1
		(d) Nervous or Difficult Children	6	8	16	18	7	55
		(e) Mental Defect	1	3	1	2	2	9
7	Diseases of of the Eye.	(a) Strabismus	8	7	7	18	7	47
		(b) Nystagmus	—	—	—	1	—	1
		(c) Conjunctivitis	5	6	3	3	2	19
		(d) Blepharitis	6	12	6	7	2	33
8	Rickets		1	9	3	—	—	13
9	Enlarged Tonsils and Adenoids.	(a) Simple Enlargement .	78	60	59	50	21	268
		(b) Great Enlargement ...	—	6	13	13	8	40
		(c) Infected	9	5	2	9	12	37
10	Otorrhoea		18	19	9	12	3	61
11	Palpable Cervical Glands		163	86	65	70	44	428
12	Carious Teeth		1	18	72	87	67	245
13	Respiratory Diseases.	(a) Bronchitis *See Below.*	—	—	—	—	*See*	*Below*
		(b) Pneumonia *See Below.*	—	—	—	—	*See*	*Below*
		(c) Asthma	—	—	—	1	1	2
		(d) Bronchiectasis	—	—	—	—	1	1
14	Anaemia		35	6	5	2	1	49
15	Malnutrition		4	36	25	17	13	95
16	Thrush		35	2	—	—	—	37
17	Acidosis		—	—	1	—	1	2
18	Phimosis		31	—	—	—	—	31
19	Undescended Testicles		2	1	1	1	2	7
20	Torticollis		1	—	—	—	—	1
21	Worms		4	5	5	10	—	24
22	Haemangiomata		14	1	1	—	—	16
23	Haematoma of Sternomastoid		2	—	—	—	—	2
24	Icterus Neonatorum		6	—	—	—	—	6
25	Breast Abscess		4	—	—	—	—	4
26	Hare Lip		—	1	—	—	—	1
27	Hare Lip and Cleft Palate		—	1	—	—	—	1
28	Goitre		—	—	—	—	1	1
29	Catarrhal Jaundice		—	—	2	—	—	2

1,530 children, 623 were entirely breast-fed, 389 were breast-fed for at least two months or had breast feeds complemented by cow's milk (usually dried) for several months, and that 518 were fed entirely on cow's milk (usually dried).

(b) **Constipation.** This occurred in eighty-three known cases, and fifty of these were under the age of one year. It was usually associated with faulty feeding and its rectification rarely gave difficulty. A few cases were troublesome, and resort had to be made to drug treatment.

2. Congenital heart disease

Nine children had this defect: seven were cases of patent interventricular septum, one was a case of pulmonary stenosis and in the remaining case it was difficult to diagnose the lesion. No case of rheumatic heart disease was found; one child gave a history of ' rheumatism ' but presented no sign of rheumatic infection.

3. Skin diseases

(a) **Seborrhoea capitis.** There were forty-six cases, all of which responded readily to treatment with liquid paraffin.

(b) **Other skin conditions.** Ninety-nine cases occurred. In the first two years of life lichen urticatus was the most frequent condition, while in the children over two years impetigo was the usual complaint. There were a few cases of infantile eczema.

4. Hernia

There were fifty-two cases of umbilical hernia and five cases of inguinal hernia. Of the fifty-two cases of umbilical hernia, fifty were found in the first few weeks of life and of these only two cases resisted treatment by strapping; two cases occurred in children aged 1–2 years and they are still under treatment. The five cases of inguinal hernia are to be treated surgically.

5. Orthopaedic defects

Thirty-six cases required treatment: eight were cases of talipes, and of these six received treatment in the first year of life. The remaining twenty-eight orthopaedic cases mostly comprised severe degrees of knock-knee or flat feet. Unfortunately, minor orthopaedic defects were not noted.

6. Defects of the nervous system

Fifty-five children were found to be ' nervous ' or ' difficult,' and in almost every case the mother was found to be over-anxious and unduly apprehensive about the child's health. Not one of these children merited treatment at a Child Guidance Clinic, and forty-one of the fifty-five were

children over the age of two years; four infants had serious convulsions and two children, in the 3–4 year age group, suffered from epilepsy. There was one case of meningocele which was uncomplicated by talipes.

There were nine cases of grave mental defect: of these one was an idiot, four were imbeciles (two being mongols), and five were probably cases of low-grade feeble-mindedness. It was impossible to detect, in the time available, the number of high-grade feeble-minded children.

7. Diseases of the eye

Defects were found in a hundred children, and of these forty-seven had strabismus. There was one case of nystagmus, nineteen of conjunctivitis and thirty-three of blepharitis. The treatment of conjunctivitis gave little difficulty; but blepharitis cases, except those treated in the first year of life, tended to become chronic unless local treatment to the eyelids, the administration of malt and oil and free grants of milk were instituted as soon as the condition arose. Unless blepharitis is treated in early life it will, in all probability, haunt the youngster through many weary winters. Its prevention is easier than its treatment.

8. Rickets

It is unpleasant to have to note that thirteen cases of active rickets were found. Only one child showing rickets was under one year, and its home conditions were bad. Nine cases occurred in the age group 1–2 years, and three in the age group 2–3 years. The significant fact found was that in all twelve cases occurring in children over the age of one year attendance at the clinics was irregular and with a long interval between each attendance. Periodic examination of these children would have prevented the onset of rickets. Much more requires to be done in the ' following up ' of absentees from Infant Welfare Clinics.

9. Enlarged tonsils and adenoids

Three hundred and forty-five children (22 per cent.) were found to be affected. In forty of these cases the tonsils were very large but were not obviously infected, and in thirty-seven cases definite inflammation or sepsis was present. The remaining 268 children had simple enlargement of tonsils only. The number of cases in this series is too small to permit any clear deduction being drawn. It can be noted, however, that the percentage of tonsils showing ' simple enlargement,' ' much enlargement ' and ' infected ' is higher in children over the age of two years than under this age. On the authority of Gray[2], tonsils were considered to be enlarged if they projected ' beyond the plane of the glossopalatine arch.' The experience of the School Medical Service supports the view that a child with simple enlargement of his tonsils suffers no complaint that can fairly be ascribed to his tonsillar enlargement; but much more would probably be learnt if it

were possible to follow a group of children from the pre-school years, having 'simple enlargement' of tonsils only, right through their school life. Sheldon[3] cites infected tonsils as a possible cause of chronic bronchitis. In the case of one child, under the age of one year, who had its throat examined monthly, there suddenly developed a severe head cold that went on to bronchitis; after the attack the tonsils became enlarged. This raises the suggestion that perhaps a fair number of the cases of simple enlargement of tonsils follow such frequent infections as the common cold. The children with large or infected tonsils require frequent supervision as most, if not all, of them will require operation later, preferably before they enter school.

10. Otorrhoea

Sixty-one children had otorrhoea. It occurred in 3·6 per cent. of children under two years, and in 4·6 per cent. of children over two years. Otorrhoea was associated with enlarged or infected tonsils in five of the eighteen cases in the first year of life and with four of the nineteen cases in the second year of life. It is a striking fact that of the thirty-seven cases of otorrhoea under the age of two years only nine had enlarged or infected tonsils. It would be interesting to know how many of the remaining twenty-eight cases ultimately showed signs of tonsillar infection. On the other hand, of the twenty-four children over the age of two years who had otorrhoea, sixteen were associated with enlarged, or obviously septic, tonsils.

11. Palpable cervical glands

Still[4] has written 'I would venture to question whether unusual palpability is necessarily a sign of disease . . . so that without any departure from health, they may be more palpable in one child than another.' In a series of 100 consecutive cases—Still does not give the ages—he found that 83 per cent. had palpable glands in the neck. Of the 1,530 children here reported on, 428 (28 per cent.) had palpable cervical glands: they were palpable in 24 per cent. of the children under two years of age and in 35 per cent. of the children over two years of age. In only twelve cases were the glands grossly enlarged; and of these four had developed abscess formation—one (in the 4–5 age group) was almost certainly tuberculous. In the case of the children under two years of age no septic area was found, from the history or from clinical examination, to account for the palpable glands; and only nineteen of the 1,014 children had carious teeth. As regards the children over two years of age, seventy-two had carious teeth. In this group it would be unwise to trust the absence of a history of any infective condition of the face or scalp as some of them had impetigo and sores and probably a good number had had these skin conditions though they denied a history of it. Even so, palpable cervical glands in children over the age of two years cannot be entirely explained by carious teeth or scalp and face sepsis. It is also true that slightly palpable cervical

glands have no influence whatsoever on the health of the child. The information obtained from this series of cases fully bears out Still's statement.

12. Carious teeth

One child under the age of one year, 18 (4·9 per cent.) of the children age 1–2 years and 226 (43·7 per cent.) of the children over two years had dental caries. The following diagram illustrates clearly the swift rise in incidence of dental caries after the age of two years, and its steadily rising incidence up to the age of five years.

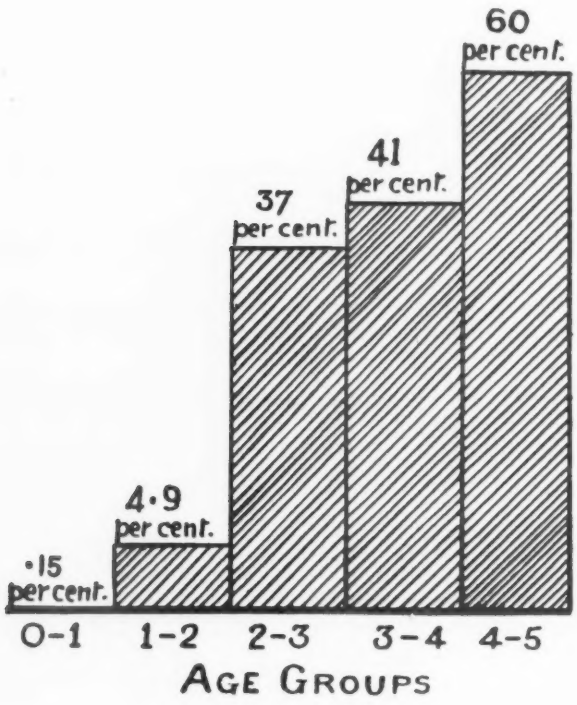

FIG. 1.

Of the 226 children over the age of two years having carious teeth, 111 were entirely breast-fed in infancy, twenty-four were fed partly on breast and partly on cow's milk, and ninety-one were fed entirely on cow's milk. In the case of the ninety-one children fed on cow's milk, their past record cards, unfortunately, did not make clear how many received cod-liver oil or other source of vitamin D, and the amount of vitamin D, as distinct from the amount of cod-liver oil, was not determined. As regards the breast-fed babes, on the evidence of Mellanby's work[5], it might reasonably be assumed—apart from the great probability that the diet of these children and the absence of

regular oral hygiene after the age of nine to twelve months more often than not would favour the development of caries—that the mothers' diet during pregnancy was inadequate, especially as regards the ' protective ' foodstuffs. On the other hand, if an insufficient amount of vitamin D in the diet of bottle-fed infants and of pregnant and nursing mothers is the factor that plays a major part in the development of dental caries, it is then rather extraordinary why carious teeth do not occur more frequently in children aged one to two years. It is interesting, too, to note that half of the children with carious teeth were breast-fed. It is doubtful if this problem of the etiology of human dental caries is yet anywhere near complete solution. The results of this investigation into the incidence of dental caries merely emphasizes the information already obtained from school medical and dental inspections.

13. Respiratory diseases

Two hundred and fifty-five children (16·6 per cent.) either had bronchitis when they were examined at the Clinic or gave a history of one or more attacks. In 187 cases it was first contracted when the child was under the age of two years, and in sixty-eight cases when the child was over two years of age. Bronchitis was the most serious and troublesome condition encountered in this investigation. In St. Helens, it seemed to be regarded by the majority of mothers as an inevitable condition of childhood and one that merely called for a ' good bottle.' Its incidence was so high, and its effect on the child's development so deplorable, that it was thought worthwhile to investigate each case. It soon became apparent that ' teething,' measles and whooping cough—causes commonly cited in the text books—were by no means the chief precursors of bronchitis. It was found that in 134 cases (52·5 per cent.) the first attack of bronchitis in the child closely followed either a catarrhal infection of the respiratory tract (colds, influenza, bronchitis) or some infective condition of the naso-pharynx (tonsillitis, sore throat) in one or more members of the family. This information was often given by the mother without direct questioning; in fact, it was the frequency of such unsolicited statements that prompted this line of enquiry in every case. In forty-seven cases (18 per cent.) the first attack of bronchitis complicated an attack of measles or whooping cough, and in only twenty-nine cases (11 per cent.) was the first attack associated solely with ' teething.' In forty-five cases (17·6 per cent.) no exciting cause could be found—' it just comes ' as one mother put it. Perhaps the best explanation that can be offered to account for these forty-five cases (and perhaps, too for the twenty-nine cases associated with teething) is that given by Pearson and Wyllie[6] ' . . . a large number of cases of chronic bronchitis—from

the evidence of the clinical history—are not primarily due to infection, but are an expression of inborn tendency to exudation: the allergic child.' In this series of cases, ' the large number of cases ' was due to infection and only a minority may have been allergic. These results are set out in table 2.

TABLE 2.

Immediate precursors of first attack of bronchitis in childhood.	Totals.
No apparent cause	45
Mother had recent attack of bronchitis	25
Father had recent attack of bronchitis	6
Grandparents had recent attack of bronchitis	2
Rest of family had recent attack of bronchitis	9
Mother had a recent sore throat or tonsillitis ...	50
Father had a recent sore throat or tonsillitis ...	6
Rest of family had recent sore throats or tonsillitis ...	1
Influenza or colds recently in family	31
Mother asthmatic	4
Following measles	38
Following whooping cough	9
Teething only	9
Total ...	255

Bronchitis in the pre-school child is a serious and recurring disease, and its prevention is a matter of real importance. There is good reason to assume that it would become much less common if every young child could be properly isolated from any member of its family having an infective condition of his or her naso-pharynx or respiratory tract. Prevention is made more difficult on account of the frequency with which the mother is, herself, the potential source of infection. It is more common in over-crowded homes, but it does exist in good homes and where there is only one child in the family. That it occurs most frequently in the cold, damp, dark days of winter is probably due to the extreme sensitivity of the child's heat-regulating mechanism to atmospheric changes and also because it is the season of the year when adolescents and adults suffer most from infectious catarrhal conditions. Adequate feeding and good housing are indispensable; but, as far as the prevention of bronchitis is concerned, they are not enough. There must be further education of the parents.

Of the 1,530 children, 209 (13·6 per cent.) gave a history of measles and 70 (4·5 per cent.) gave a history of whooping cough. Eighty-nine children (5·8 per cent.) had one or more attacks of pneumonia; two suffered from asthma, and one from bronchiectasis. Though not respiratory diseases it is interesting to note that seventeen children (1·1 per cent.) had scarlet fever and seven (0·45 per cent.) had diphtheria; the high incidence of measles and whooping cough compared to the low incidence of diphtheria and scarlet fever in this series of cases is striking. In compiling these results the age of onset of measles, whooping cough and pneumonia was not noted when the children over two years of age were examined. It was found that 188 of the children over two years

of age gave a history of either measles or whooping cough, and fifty-seven gave a history of pneumonia; but it was not determined if these diseases were contracted before or after the age of two years. This omission was only appreciated when these results were being analyzed. A further point that was not investigated was whether the incidence of bronchitis following measles and whooping cough was higher in those children who had a previous attack of bronchitis than in those who had no previous attack. No case diagnosed as pulmonary tuberculosis was found.

14. Anaemia

Forty-nine (3·2 per cent.) children were anaemic when examined. Of these, thirty-five (5·3 per cent. of children under one year) were children under one year. In view of Mackay's[7] work, this is a surprisingly low figure. Here the examination was purely clinical; the figures would, probably, have been higher if more precise methods were used.

15. Malnutrition

Ninety-five children (6·2 per cent.) were found to be undernourished. Of the 652 children under one year, only four (0·6 per cent.) were malnourished, whilst of the 878 children over one year ninety-one (10 per cent.) were undernourished. All the children who were not breast-fed received dried cow's milk at the Clinic for the first twelve months of life. The higher incidence of undernourishment in the later groups makes it clear that if dried milk were not supplied the number of children under one year showing signs of undernourishment would, undoubtedly, have been greater. These cases were well marked, all requiring extra nourishment. This evidence, together with the number of children showing dental caries and the fact that in eighty-two cases the nutrition of the mother was very poor, all suggested an enquiry into the social background of these children.

The social environment.—In 1,214 cases the full economic condition was known. The mother, at the Clinic, completed a form setting out the number of children in the family, their ages, the gross amount of the family's earnings and the amount of rent paid. The father had to sign another form giving the amount of his wages and/or other source of income for the previous four weeks. To prevent abuse, these figures were frequently checked by direct reference to employers. It soon became known that this procedure was being adopted and accurate wage returns were made. It was found that the father was employed in 772 cases and unemployed in 442 cases. Table 3 summarizes the findings:—

TABLE 3.

	Duration of Unemployment (442 persons).					
Employed	½–1 year	1-2 years	2-3 years	3-4 years	4-5 years	5+ years
772	38	78	64	72	66	124
					Totals ...	1,214

In assessing the financial position of each family the man-value of each family was worked out; and for this purpose the man value caloric coefficients, set out in the Report on Nutrition[8] by the Nutrition Committee of the British Medical Association, was adopted. Also, the minimum cost of food per man-value per week, estimated at 5s. 11d., by that Committee was here employed. In addition to food and shelter a family requires for the maintenance of health a sufficient amount of fuel, lighting, clothing, and cleaning materials. To cover these essentials different authorities have suggested different scales, but the scale set out in the 'Social Survey of Merseyside'[9] is a reasonable one and it was used in this investigation. Table 4 gives this scale of needs.

TABLE 4.

MERSEYSIDE SURVEY.

MAN VALUE.	FUEL.	CLOTHES, CLEANSING, LIGHT, ETC.	TOTAL.
1·8	2s. 5d.	2s. 8d.	5s. 1d.
2·2	2s. 5d.	3s. 8d.	6s. 1d.
3·4	2s. 5d.	5s. 8d.	8s. 1d.
4·9	2s. 5d.	7s. 9d.	10s. 2d.

When these minima were applied to each family, after deducting the amount paid in rent from the total earnings, it was found that of the 1,214 families investigated 364 (30 per cent.) had incomes insufficient to cover the bare necessities of life. As rent, heating and lighting must be paid for, it was found that they were obtained at the expense of the amount that should have been paid for food. Table 5 gives this information.

TABLE 5.

	EMPLOYED	UNEMPLOYED	TOTALS
INCOME SUFFICIENT	669	181	850
INCOME INSUFFICIENT	103	261	364
TOTALS ...	772	442	1,214

In 367 cases (30 per cent.) the amount paid in rent was less than 20 per cent. of the family income; in 667 cases (55 per cent.) the rent was between 20 per cent. and 30 per cent. of the family income, and in 180 cases (15 per cent.) it took more than 30 per cent. of the family income.

Incomes were found to be insufficient most frequently when the family was large. Table 6 gives the size of the families.

TABLE 6.

NUMBER OF CHILDREN IN FAMILY.

TOTAL	1	2	3	4	5	6	7	8	9	10 AND MORE
1,214	311	299	207	138	100	69	40	33	11	6

In seventy cases (5·7 per cent.) the mother's management was scandalously poor, and no amount of propaganda would have had the slightest chance of permanently improving it. In at least thirty of these cases the presumption was that the mother was feeble-minded.

However regarded, the economic background of these children's lives is a sad one. Even in those cases in which the family income was deemed sufficient, the balance, after paying for essential needs, was often pitiably small. And in 364 families the income was insufficient to buy the minimum amount of food necessary for health. This problem of undernourishment is a vexed one and one difficult of solution. To-day it is, perhaps, the chief problem that preventive medicine has to face. 'The evidence that Malnutrition exists is conclusive . . . the physical condition of a large part of the human race is still far below the accepted standard and this inferiority is largely due to imperfect nutrition.'[10] Too often is undernourishment ascribed to bad management on the part of mothers; the adoption of this view merely clouds the issue, though it provides an easy excuse for ignoring the larger problem. As far as this investigation was concerned, it was found that bad management played but a minor part, thus confirming the opinion of the Nutrition Committee of the British Medical Association[8].

'. . . the average housewife, with no expert knowledge of calories, proteins, etc., does, in fact, purchase by rule-of-thumb methods foodstuffs which broadly approximate to dietaries considered by physiologists to be satisfactory. The above statement is subject to her purchasing powers proving adequate to the needs of her family. When the amount of money available for the purchase of food is not enough to enable the housewife to buy what she needs (and without understanding the scientific reasons she usually wants the right things in approximately the right quantities) she must economize in certain directions. Experience has taught her that she must avoid complaints of hunger and of 'emptiness' from her family, so she buys a smaller proportion of expensive proteins and fats (such as butter) and a higher proportion of cheap carbohydrates—usually bread and, according to their seasonal price, potatoes.'

And the probability is that it is because the housewife buys so little first-class protein and 'protective' foodstuffs that in this investigation it was found that only 47 per cent. of mothers were able wholly to breast feed their babes, that 44 per cent. of the children over two years of age had carious teeth, that 10 per cent. of the children over one year were undernourished and that 5 per cent. of the mothers showed very poor nutrition. Knowing that in the case of at least 364 families an adequate diet was unobtainable for financial reasons it is hard to explain why only ninety-five children and eighty-two mothers showed poor nutrition. If all the mothers had been carefully examined the total would, undoubtedly, have been higher, but the larger number would not have been anywhere near 354; either the dietetic opinion of the physiologists is wrong or clinical methods of investigation are imperfect.

Conclusions

To state, without qualification, that 60 per cent. of the 1,530 children here examined had physical defects would be to give a grossly distorted picture of the health of the pre-school child. If it is agreed that (1) unusual palpability of neck glands is not necessarily and, in fact, rarely is, a sign of disease and (2) that simple enlargement of the tonsils has no adverse effect on the child's health (and until the contrary is proved this can be assumed to be the correct view) then only a minority of pre-school children will be found to have physical defects, other than carious teeth. But a substantial minority (16·6 per cent.) have had or still have attacks of bronchitis that in more than 50 per cent. of cases followed an infective condition of the naso-pharynx or respiratory tract of some other member of the family. Malnutrition was a problem of importance, but a problem of much greater importance was that 30 per cent of 1,214 families, whose economic state was specially investigated, had incomes insufficient in amount to buy the food stated by the Nutrition Committee of the British Medical Association to be the minimum essential for health. Carious teeth became a problem only after the age of two years, but then it became a serious one and one that increased with age. Though only 2 per cent. of the cases had blepharitis this condition was difficult to cure and tended easily to recur. In 5 per cent. of the children the tonsils were greatly enlarged or infected and merited surgical treatment. Though cervical glands were palpable in 28 per cent. of the children, they only became a clinical problem in 0·78 per cent. of cases. Otorrhoea was present in 3·9 per cent. of the children, and 16 per cent. of the children under one year of age had to have their feeding investigated.

Though an increasing and more regular attendance at the Infant Welfare Centres will help to improve and foster the health—and thereby the happiness—of the pre-school child, it is yet felt that no great advance in the standard of health of the citizen of to-morrow can be expected until the problem of adequate feeding of all the children in the community is scientifically and thoroughly tackled.

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THE EFFECT OF BOILING ON THE NUTRITIVE VALUE OF MILK

BY

STANLEY GRAHAM, M.D., AND NOAH MORRIS, M.D.

(From the Department of Paediatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

It is admitted on all sides that untreated milk, no matter of what quality, may act as a carrier of infective material. In this connexion it should be emphasized that the tubercle bacillus is but one of the pathogenic organisms liable to be so transmitted. Smith[3] in Aberdeen found that of 183 samples of milk 17 contained brucella abortus while Pullinger[2] in 101 samples from 45 tested herds found brucella in 45 and it is generally recognized that epidemics of such diseases as scarlet fever, diphtheria and typhoid fever can arise from infected milk. It would appear, therefore, that it would be of advantage if, other things being equal, milk could be rendered free of pathogenic organisms. There are three main objections brought forward against sterilization of milk. It is urged that the universal adoption of sterilization by providing a germ-free supply would remove the incentive to the purchase of a high-grade supply from certified herds and that there would be no encouragement for farmers to go to the expense of maintaining such herds. It should, however, be possible to support the breeding of high-grade tubercle-free cattle and at the same time prevent the dissemination of disease by milk. Secondly it is held, and with justice, that germ-free milk does not necessarily mean either good-quality or even clean milk. The general public must be made to realize that three things are necessary for milk, (1) that it should be rich in fat and vitamins, (2) that it should not contain foreign material even if it is sterile, and (3) that it should be free of pathogenic organisms. Thirdly, it is maintained that sterilization alters the nutritive value of milk. This is the most fundamental objection and the following experiments are an attempt to throw light on this aspect of the problem.

In deciding whether or not sterilization alters the biological value of milk as a foodstuff for man it is preferable to test this on the human subject. If experimental animals are used it is essential that they should be observed during a period of life corresponding to that which it is desired to study in man. Even when the effect of sterilized milk is tested on the human subject it is necessary to take into account the possibility of natural fluctuations of growth unless large numbers are studied. Another source of error in such experiments occurs when the sterilized and raw milks do not come from the same source since the differences which may occur may be due not to differences in the treatment of the milks but rather to differences in their quality prior to any treatment which they may have undergone.

Even when all these difficulties have been surmounted there is still to be faced the question as to what is to be the test of nutritive value. The best test is probably the rate of increase in height and weight but this cannot be taken as an index, since it varies from time to time and any investigation must include very large numbers in order to overcome these fluctuations. Even in large scale field experiments such as those in Lanarkshire and America difficulties have arisen both in their conduct and interpretation. Here the problem is approached from another angle and the attempt is made to discover if heat treatment of milk causes any alteration in the retention of minerals, nitrogen and fat. This test is at any rate as objective as can be devised but it is not to be inferred that nutrition can be gauged merely by the amounts of minerals and nitrogen that are retained. This procedure was adopted because few satisfactory experiments have been carried out on the human subject with the object of determining if heat treatment of milk causes any alteration in the retention of its constituents.

In a previous communication[1] experiences with two infants fed exclusively on milk were reported. In it were given the results of balance experiments with raw and boiled milk respectively of one week's duration with suitable pre-periods. The retentions of calcium, phosphorus, nitrogen and fat were determined. Briefly, no evidence was obtained that the boiling of milk affected adversely the retention of these substances. Indeed, lower retention values for the first three were obtained while the infants were on raw milk; in the case of fat, the retentions were virtually the same. The object of the present communication is to record the results obtained from two older children who were on a diet not exclusively of milk.

Method and results

Two children of ten-and-a-half and seven-and-a-half years respectively were given the diet noted in table 1. About 50 per cent. of the caloric value of the diet and 70 per cent. of the total protein were supplied in the form of milk. The caloric intake as well as that of protein, minerals and fat was ample.

TABLE 1

JAMES S., aged 10 yr. 5 mth.; weight 26·6 kgm. Milk 1,250 c.c., sugar 44 gm., bread 120 gm., butter 10 gm., orange juice 30 c.c., banana 100 gm., water 300 c.c. (protein 57 gm., fat 57 gm., carbohydrate 194 gm.). Total intake 1,526 calories.

PETER T., aged 7 yr. 7 mth.; weight 23·2 kgm. Milk 1,000 c.c., sugar 44 gm., bread 120 gm., butter 10 gm., orange juice 30 c.c., banana 100 gm., water 300 c.c. (protein 48 gm., fat 47 gm., carbohydrate 182 gm.). Total intake 1,360 calories.

PERIOD (7 DAYS)	I	II	III	IV	V
James S.	Boiled milk	Raw milk	Raw milk	Boiled milk	Boiled milk
Peter T.	Raw milk	Boiled milk	Boiled milk	Raw milk	Raw milk

Milk from the same source was utilized throughout the investigations. During the sterilized milk period, the milk was boiled for three minutes. Boiling was used in preference to commercial pasteurization in order to make certain that all the milk used came from the one source. After a period of not less than five days on the diet urine and faeces were collected for seven days. Thereafter the milk was changed from raw to boiled in one case and from boiled to raw in the other. This was continued for a fortnight when the milk was again changed to the first variety for another fortnight. Each child was, therefore, observed for a period of five weeks; (1) a week on raw or boiled milk, (2) two weeks on boiled or raw milk and (3) two weeks on raw or boiled milk.

Calcium, phosphorus and nitrogen were estimated in the faeces, urine and aliquot portions of the various articles of the dietary. The fat content of the faeces and the diet was also determined. The results are given in tables 2 and 3.

JAMES S.

TABLE 2.

PERIOD.	RETENTION (MGM. PER KGM. PER DAY)			FAT (PERCENTAGE ABSORPTION).
	CaO	P_2O_5	N	
I. B.	27·9	45·9	50·3	96·4
II. R.	30·1	50·2	41·7	96·9
III. R.	28·2	38·4	52·6	94·5
IV. B.	32·2	44·8	46·4	95·7
V. B.	31·7	45·0	40·0	93·6
AVERAGES.				
I. B.	27·9	45·9	50·3	96·4
II. / III. R.	29·2	44·3	47·2	95·7
IV. / V. B.	32·0	44·9	43·2	94·7

B = Boiled Milk. R = Raw Milk.

PETER T.

TABLE 3

PERIOD	RETENTION (MGM. PER KGM. PER DAY)			FAT (PERCENTAGE ABSORPTION)
	CaO	P_2O_5	N.	
I. R.	13·5	27·1	19·6	95·5
II. B.	47·3	45·7	24·2	98·2
III. B.	-23·5	1·8	15·1	91·9
IV. R.	43·9	25·4	19·3	98·0
V. R.	-11·9	23·1	18·1	92·9
AVERAGES				
I. R.	13·5	27·1	19·6	95·5
II. / III. B.	11·9	23·8	19·4	95·1
IV. / V. R.	16·0	24·3	18·7	95·5

B = Boiled milk. R = Raw milk.

Comment

With James S. the retentions of phosphorus, nitrogen and fat showed no significant variations during the whole period of observation. Calcium retention showed a slight increase during the last two weeks on boiled milk. With Peter T., however, it will be observed that the change from raw to boiled and from boiled to raw milk produced in each case a great increase in the retention of calcium and phosphorus due to a great decrease in faecal output. This increased retention was only apparent as it was counterbalanced by the increased faecal output during the succeeding week. When the raw milk results are taken together and compared with the figures obtained during the two weeks on boiled milk it is clear that the retention of CaO and P_2O_5 during the consumption of boiled milk is only slightly lower than when raw milk was taken. It would appear that the change from raw to boiled milk and vice versa led to temporary periods of constipation. This is an observation which requires to be emphasized in the performance of retention experiments. It is generally held that a period of a week is sufficient for the determination of retention. These observations indicate that in some cases a fortnight may be necessary in order to prevent a temporary alteration producing a fallacious result.

In testing the value of sterilized milk in a mixed dietary it is necessary to make clear various methods which may be used. In the first place the milk may form either the main part or only a small fraction of the diet. Secondly, the total intake of one or more constituents of the diet may be ample or barely sufficient. Thirdly, the period of observation may be relatively short over a period of a few weeks or extend for months or years.

The results recorded here indicate that there is no evidence that over short periods the boiling of milk impairs either its absorption or utilization, when there is an ample supply of proximate principles and minerals and when the caloric intake is adequate. It still remains possible that over long periods or/and when the intake is no more than sufficient, the sterilization of milk might make a difference to the retention of essential substances. So far, however, satisfactory proof of this is lacking.

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NUCLEAR JAUNDICE IN NEONATAL (UMBILICAL) SEPSIS WITH JAUNDICE*

BY

A. BIEMOND, M.D., AND S. VAN CREVELD, M.D.

It is a well-known fact that after familial jaundice in the new-born there not rarely remain certain cerebral symptoms which are related to a particular localization of the icteric staining in the brain substance, especially in the basal ganglia.

The first description of icterus gravis neonatorum was given by Orth[1], and the familial character was stressed by Schmorl[2]. In recent years a number of articles on this subject have appeared. In America it was discussed extensively by Zimmermann and Yannet[3], and recently by Astrachan[3a], in England by Hawksley and Lightwood[4], in France by Péhu, Brochier and Wang[5] and in Holland by C. de Lange[6]. The relationship of icterus gravis neonatorum to hydrops foetalis and congenital anaemia has been studied recently by Diamond, Blackfan and Baty[7] and by Parsons, Hawksley and Gittins[8].

On the cause of the peculiarly localized icteric staining in the brain as well as on the etiology of icterus gravis neonatorum there exist different opinions which have been summarized recently in the articles of Zimmermann and Yannet, of Hawksley and Lightwood, and of Péhu, Brochier and Wang. Next to the question of the etiology of icterus gravis neonatorum and of nuclear jaundice occurring with it, two other questions related to this subject have occupied the attention of both older and more recent investigators. One is the treatment of icterus gravis neonatorum which has been and still is a widely-discussed problem. The other question which is to be specially discussed in the present article is whether nuclear jaundice in the new-born is a peculiarity of icterus gravis neonatorum.

As regards the last-mentioned question there are no cases with autopsy records which can help to solve the problem. There only exists the clinical description of a case of neonatal septic jaundice with extrapyramidal disturbances in motility, given by C. de Lange[9] in which it is suggested that in this form of neonatal jaundice icteric staining of the basal ganglia may also occur. However, no autopsy was possible in this case.

Case Records

Recently it has been possible to observe two infants in whom there occurred neonatal umbilical sepsis with jaundice and typical extrapyramidal disturbances in motility pointing to the existence of a nuclear jaundice. Both infants died after some months; in both an autopsy was performed and the presence of a previous nuclear jaundice could be demonstrated.

* From the Propaedeutic Clinic and the Anatomical Laboratory of the Neurological Clinic, University of Amsterdam.

Case 1. E. C., a male infant, was born spontaneously after a normal pregnancy at full time with a birth-weight of 2,700 gm.

FAMILY HISTORY. The parents were healthy and the patient was the sixth child. The first three children were born at full time and are healthy. Then twins were born of which one child is alive and healthy, the other having died at the age of three days. The exact cause of death of this infant is unknown, but it may have been icteric soon after birth.

CLINICAL HISTORY. The patient was taken into the Propaedeutic Clinic when four days old. He had been ill one day. He was sleepy, did not suck, did not cry, had loose stools, black and yellow in colour, was whimpering all the time. According to the parents he became jaundiced shortly after birth. On examination in the hospital when four days old, the infant gave the impression of being seriously ill, the skin and mucous membranes were strongly jaundiced; the infant cried normally. There was conjunctivitis of both eyes, the temperature was 39° C. There existed an umbilical infection with a red coloured swelling at the insertion of the umbilical cord which had not completely separated. The abdominal wall around the umbilicus was swollen and muco-purulent fluid was discharged from it. The liver was slightly enlarged, the spleen was not felt. The urine contained urobilin and bilirubin, together with a trace of albumin. In the sediment were many leucocytes and erythrocytes.

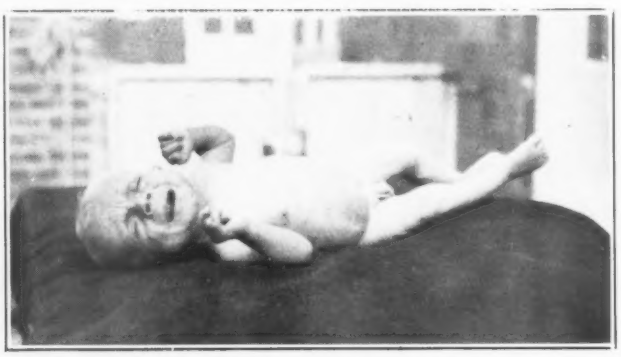

FIG. 1.—Case 1.

The infant did not take food and tube feeding was necessary. On the fifth day of life distinct symptoms of rigidity were already noted in arms, legs and neck. The umbilical infection slowly subsided over some weeks, but it took about six weeks before the jaundice had disappeared and with it also the enlargement of the liver disappeared. During the time when the jaundice was still severe, the stools for several days were acholic. The fundus oculi was examined several times and found to be normal, but the impression obtained during the further course of the disease was that the infant could not see. The neurological symptoms remained nearly unchanged for several months and had a distinct extrapyramidal character. The head was pushed into the pillow with tendency to opisthotonus. There was strong hypertonia especially of the arms with clasp-knife phenomenon, a general lack of motility, monotonous crying, ' mumbling ' of the lips and peculiarly irregular respiration. The hypertonia was especially pronounced at the wrists. In the legs it was distinctly less than in the arms. At the temporomandibular joints there was also distinct hypertonia. The arm reflexes were present and equal on both sides. The abdominal reflexes were present; the knee reflexes present and equal. The Achilles reflex was only present at

right side. The pupils reacted to light. The corneal reflexes were present. The child reacted to pain-stimulation over the whole body. A film was made of the movements of the infant which showed clearly the typical disturbances of an extrapyramidal disease. The accompanying figure 1 is taken from this film. The temperature, with the exception of the first two days after admission remained normal during the whole further course of the illness.

The general condition in the beginning improved slightly and then remained about the same for a long time. The stools were soon normal. Tube feeding was omitted after about one week. Some days after admission the infant on three occasions received an intramuscular injection of 10 c.c. of the father's blood. It took more than two months before bilirubin had disappeared from the urine. The sediment of the urine soon became normal. At the age of three months the infant died from bronchopneumonia.

LABORATORY FINDINGS. In the presence of a severe jaundice special attention was paid to the blood picture. During the first weeks there was a strong leucocytosis. The results of the blood investigation at different times are given in table 1. An important fact was that nucleated cells were never found in the blood, even during the first week of the observation.

TABLE I.

PAT. E.C.

AGE	RED CELLS PER C.MM.	HAEMOGLOBIN (SAHLI) PER CENT.	WHITE CELLS PER C.MM.	ERYTHROBLASTS	BLOOD PLATELETS	ICTERIC INDEX	V. D. BERGH	RETICULOCYTES PER CENT.
4 days	—	—	28,300	0	normal	—	—	—
13 ,,	4,720,000	113	36,100	0	normal	90	dir. + indir. +	—
23 ,,	3,360,000	68	28,900	0	normal	50	ditto.	14½
1 month	—	66	14,100	—	—	40	—	—
1½ ,,	—	68	—	—	normal	40	—	11
2 ,,	4,200,000	71	16,100	0	normal	5	—	—

Further, the increase in the mean diameter of the erythrocytes, found by the Price-Jones method in cases of icterus gravis neonatorum during the first week of the illness[10a], was absent in this case and during the further course a greater diminution in mean diameter occurred than in the normal child, propably due to severe haemolysis*. The decrease of the haemoglobin content as compared with normal figures was only small; there was no question of a hyperchromic anaemia. A decrease of thrombocytes as often found in icterus gravis neonatorum was absent during the whole course of the disease and there was, further, no haemorrhagic tendency. The number of reticulocytes, nearly always increased in icterus gravis neonatorum during the first weeks, was normal here. As regards the van den Bergh reaction it was directly and indirectly positive, as is generally the case in icterus gravis neonatorum. The Wassermann and Sachs-Georgi-tests in the blood of the infant and of the parents were negative.

The possible effect of the septic jaundice on the liver was investigated during life by performing some liver function tests. The protein spectrum of the blood plasma was studied twice, at the age of two-and-a-half months

* Compare the same findings in icterus gravis.

and directly before death. The results are given in table 2, which also contains the results obtained in some control infants of about the same age and in the second patient. It is noteworthy that a definite increase was noticed even at this age in the globulin content, which resembles the fairly constant increase of globulin in parenchymatous liver affections. The Takata-Ara test and the sedimentation rate of the erythrocytes, the results of which show a definite parallelism to the globulin content, were also increased in this infant. As regards the increased sedimentation rate the relation to the increased globulin content may be deduced from the fact, that it was about the same in the defibrinated blood as in the non-defibrinated blood. The blood-cholesterol was normal. The fasting blood sugar at the age of ten weeks was 0·081 per cent.; the galactose-test (investigation of urine) and the fructose-test (blood-sugar curve) at the time gave normal figures.

TABLE 2.

PROTEIN-SPECTRUM.

	TOTAL PROTEIN PER CENT.	FIBRINOG. PER CENT.	GLOBULIN PER CENT.	ALBUMIN PER CENT.
Pat. E.C., 2½ months	61.2	—	18.9	42.3
,, nearly 3 months	67.8	4.1	23.2	40.5
Healthy baby	—	4	—	—
,, ,, ...	59.8	—	16.1	43.7
,, ,, ...	61.2	—	14.1	47.1
,, ,, ...	50.3	—	10.2	40.1
Pat. M.H., 13 days	57.9	—	18.3	37.2

Pat. E.C., 12 weeks. Takata-Ara test—positive.
Sedimentation rate 12, in defibrinated blood also 12 (micro-method ; normal value 6-8 mm.)
Laevulose test normal.

Pat. M.H., 13 days. Takata-Ara test—negative.
Galactose test normal.

POST-MORTEM EXAMINATION at the Pathological-Anatomical Institute (Prof. H. T. Deelman), twenty-four hours after death. Pathological details of the internal organs noted were:—Lobular pneumonia, haematoma of cardiac valves, left-sided hydronephrosis. As concerns the liver and spleen the following was communicated:—

The liver was somewhat enlarged (170 gm.), had a firm consistency and sharp edges. The umbilical vein for the greater part was obliterated, as also the ductus venosus. The capsule was humid, glossy, dark brown, with no haemorrhages. The cut surface was smooth, moist, with liver markings visible. The microscopical investigation of frozen sections showed that there was a slight central fatty change. The portal spaces contained some young connective tissue cells. No myeloid tissue was seen. In some of the bile ducts there were bile thrombi; in some of the liver cells, as well as in some of the portal spaces, there was a fine-granular pigment which did not give a positive iron reaction. Glycogen staining did not show any abnormalities.

The spleen was slightly enlarged, weight 20 gm. The capsule was smooth, glossy, spotted and blue-red. The cut surface was regular, moist, dark red with small grey follicles and no trabeculae. Microscopical investigation showed normal follicles; the trabeculae showed no abnormalities. Brown pigment was present in the pulp cells. From the investigation of preparations stained to demonstrate iron, it appeared that there was a fair degree of siderosis.

MORBID ANATOMY OF BRAIN (Anatomical Laboratory of the Neurological Clinic). Macroscopical investigation: the cerebrum was pale, not yellow, very soft, symmetrical and externally showed no abnormalities. After section it appeared that cerebrospinal fluid was present in normal amount; it was uncoloured. There was no hydrocephalus. On section no icteric staining of the basal ganglia was seen, but on inspection with a magnifying glass it appeared that striation of the globus pallidus was absent at both sides.

Microscopical investigation: the cerebrum was investigated by serial sections after Kulschitzky-van Gieson and preparations of different parts of the cerebral cortex and of the basal ganglia were stained after Nissl, and with haematoxylin-eosin. To some portions of the basal ganglia staining with Sudan III and Penfield and Holzer's method were further applied. The study of the serial sections showed that there was much demyelinization of the globus pallidus (fig. 2) and of the corpus subthalamicum (fig. 3) on

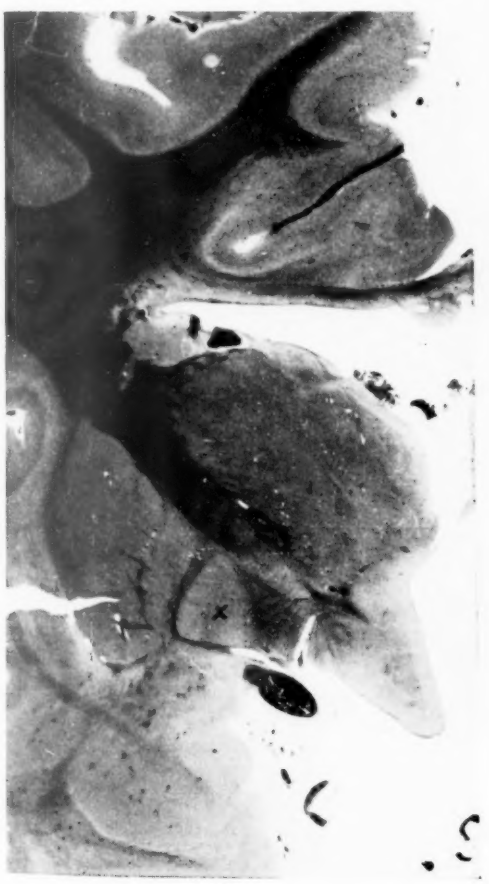

FIG. 2.—Demyelinization of the globus pallidus (×) in case 1. (Kulschitzky-staining.)

FIG. 3.—Demyelinization of the corpus subthalamicum (×) in case 1. (Kulschitzky-staining.)

both sides. The demyelinization was greatest at the internal segment of the globus pallidus and appeared to increase in the occipital direction. The putamen only showed slight demyelinization, whereas the nucleus caudatus proved to have normal fibre proportions. From the cell preparations it appeared that in the regions of demyelinization there was a severe loss of ganglion cells, followed by a moderate gliosis. It was striking that generally the demyelinization was more intense than the loss of cells; this was especially evident on inspection of the corpora subthalamica, which still showed several well-formed ganglion cells, whereas the myelin sheaths had almost completely disappeared. No signs of inflammation, haemorrhages, nor accumulations of pigment or fat were seen. The cell preparations of different parts of the cortex did not show definite changes. The substantia nigra was normal. The investigation of the fibre preparations in serial sections showed that the corpus callosum, especially its frontal part was abnormally thin, and it was hardly possible to discover the fornices. The explanation of the latter fact was made more difficult by the incomplete myelinization of these parts of the brain in the young infant. Comparison with the brain of an infant of about the same age indicated, however, that here was a definite hypoplasia of the corpus callosum and of the fornices.

Case 2. M. H., a female infant, born spontaneously after a normal pregnancy, at full time, had a birth-weight about 4,000 gm. There was no asphyxia and no icterus at birth.

FAMILY HISTORY. Mother was healthy; father suffered from bronchial asthma. Two other children were normal. There had been no miscarriages.

CLINICAL HISTORY OF THE PATIENT. The patient was taken into the Propaedeutic Clinic when three days old. Twelve hours after birth the father had noticed that the infant was slightly icteric. On the following day the jaundice had increased and subsequently deepened. On the second day of life the infant refused to suck. On examination in the hospital the baby was deeply icteric, of an orange-yellow colour, and somewhat drowsy. Distinct rigidity was noted in both arms. The temperature was 37·5° C. The heart and lungs were normal. The liver was slightly enlarged, the spleen not palpable. The umbilicus was thickened, red and infiltrated; above the umbilicus there was infiltration of the abdominal wall. The stools were normal. The urine was deep dark brown. Thus also in this case there existed a distinct umbilical infection. The urine contained bilirubin, together with a trace of albumin, and some leucocytes and erythrocytes in the sediment. The child was given fluid subcutaneously and frequent small feeds.

On the second day after admission the infant was very ill; the rigidity had extended. The stools were undigested and slightly pale. The umbilicus was much infiltrated, the liver more enlarged, the spleen not palpable. The fontanelle was not depressed. There were some haemorrhagic spots on the face.

On the third day after admission the jaundice was extremely severe. The neurological picture showed a varying hypertonia, especially of the arms. This hypertonia was strongest in the joints of wrists and fingers; the hands were constantly clenched (fig. 4). The neck and back were stiff and there was a tendency to opisthotonus. The patellar reflex was present on both sides. The Achilles reflex was absent. The reflex of Babinski was present on both sides which is normal at this age. No abdominal reflexes and no arm reflexes could be obtained. The pupils reacted normally. Fairly strong dermographia was present. Pain-stimulation produced a reaction over the whole body.

It took a long time (about six weeks) before the jaundice disappeared; the umbilical infection also slowly cleared up. The neurological symptoms

remained constant. The fundus oculi in this patient also showed no abnormalities; this infant also probably could not see. At the age of four months the infant died from bronchopneumonia. The liver had remained palpable two finger breadths below the costal margin; the spleen was also slightly enlarged.

FIG. 4.—Case 2.

LABORATORY FINDINGS. The stools contained bile pigments and the urine contained bile pigments and a trace of albumin for several weeks. The results of the blood examinations at different times in this case are given in table 3. From this it appears that also in this case there was no

TABLE 3.

PAT. M.H.

AGE	RED CELLS. PER C.MM.	HAEMOGLOBIN (SAHLI) PER CENT.	WHITE CELLS PER C.MM.	ERYTHROBLASTS	BLOOD-PLATELETS	ICTERIC INDEX	V. D. BERGH	RETICULOCYTES PER CENT.
3 days	—	—	—	0	normal	—	—	—
4 ,,	3,840,000	86	16,200	0	normal	—	—	—
7 ,,	—	—	—	0	—	—	—	—
13 ,,	3,350,000	65	24,000	2	normal	100	dir. +	5
25 ,,	—	57	17,000	0	normal	60	indir. + ditto	6
6 weeks	2,540,000	59	16,200	2	slight increase	20	—	4
*8 ,,	2,990,000	67	17,600	0	normal	—	—	2½
3 months	3,670,000	80	8,400	0	normal	—	—	6

* Had been given 300 mgm. of reduced iron for 1 week.

question of an erythroblastaemia. The blood platelets were not increased; the number of reticulocytes was not abnormally high. The mean diameter of the erythrocytes on the day of admission was slightly decreased as compared with normal figures; an increase as recorded in icterus gravis neonatorum was thus absent. The van den Bergh reaction was directly and indirectly positive. The Wassermann and Sachs-Georgi tests in the blood of the infant and in that of the parents were negative. The protein spectrum at the age of fourteen days also here showed a slight increase of the globulin content. The Takata-Ara test was negative, as also was the result of the galactose test. A blood culture at the age of twenty-two days had a negative result. The morphological blood study of the parents gave normal results, the fragility of the red blood corpuscles was also normal in both parents. In view of the rare occurrence of cystic changes in the bones in icterus gravis neonatorum (Braid[11]) an x-ray study of the bones was made in this second patient, but no changes were found.

A POST-MORTEM EXAMINATION was made twenty-four hours after death, at the Pathological Institute. The pathological diagnosis of bronchopneumonia was made. As concerns the liver and spleen the following was communicated:—

The liver was slightly enlarged (250 gm.), had a normal shape and elastic consistency; the colour was brown-violet. The capsule did not show abnormalities. The cut surface had a dark yellow-brown colour with normal design. The vessels and bile ducts did not show abnormalities. The microscopical examination of sections stained with Sudan III demonstrated a fatty change consisting of large and small droplets and principally of peripheral localization. In the sections stained with haematoxylin-eosin there was a fairly large amount of bile pigment between the cells. Spread all through the sections there was also much blood pigment (iron staining). Nowhere could be seen myeloid tissue, nor signs of fibrosis.

The spleen also was slightly enlarged (weight 18 gm.). The capsule was smooth, glossy, moist and transparent. On the cut surface the follicles were visible in the normal way. The microscopical investigation demonstrated that the spleen contained much blood; blood pigment also could easily be shown here.

MORBID ANATOMY OF THE BRAIN (Anatomical Laboratory of the Neurological Clinic).

Macroscopical investigation. The brain in this case also did not show abnormalities on external inspection. After cutting the brain and inspection with magnifying glass it appeared however that there existed a slight icteric staining of the globus pallidus and of the corpus subthalamicum on both sides. Also here it appeared that the striation of the globus pallidus was absent on both sides. There was no hydrocephalus and the cerebrospinal fluid was uncoloured.

Microscopical investigation. The cerebrum was investigated in serial sections stained after Weigert Pal–van Gieson. Nissl and haematoxylin-eosin preparations were also prepared from several pieces of the cerebral cortex and of the basal ganglia. Finally some pieces of the basal ganglia were stained by Sudan III and by the method of Penfield and Holzer. The pictures obtained showed a striking resemblance with those of case 1. Also here there existed a marked demyelinization of the globus pallidus (fig. 5) (which was most striking in the medial segment), and of the corpus subthalamicum (fig. 6) on both sides, whereas the putamen and nucleus

FIG. 5.—Demyelinization of the globus pallidus (×) in case 1. (Weigert-Pal-staining.)

FIG. 6.—Demyelinization of the corpus subthalamicum (×) in case 2. (Weigert-Pal-staining.)

caudatus remained free. Here also there existed in the demyelinized regions a marked loss of ganglion cells (with moderate gliosis), which was however far less than the loss of fibres. Signs of inflammation as well as haemorrhages and fatty changes were absent.

The similarity with case 1 was also evident as regarded the structure of the corpus callosum and fornices which here also showed a slight but undeniable hypoplasia.

Comment

I. In both infants there existed an analogous morbid picture with nearly the same course of the disease. The most important characteristics of this morbid picture may be summarized as follows:—

(a) Development of an extrapyramidal neurological disturbance in connexion with a severe jaundice which arose shortly after birth.

(b) Absence of cases of icterus gravis neonatorum, of hydrops foetalis or of anaemia gravis of the new born, in both families.

(c) Definite umbilical infection.

(d) In both cases erythroblastaemia and at the autopsy also erythroblastosis which occur in the early stage of nearly every case of icterus gravis neonatorum were absent. The number of thrombocytes was not decreased, the number of reticulocytes was not increased, and increase of the mean diameter of erythrocytes, recorded in the early stage of icterus gravis, was absent in both cases*. These and other points of difference between the clinical and laboratory findings in the two patients with icterus gravis neonatorum are given in table 4.

TABLE 4.

TO SHOW THE SIMILARITY TO AND DIFFERENCES FROM ICTERUS GRAVIS NEONATORUM OF THE CASES HERE DESCRIBED.

	Patient E.C.	M. H.
Icterus present at birth or arising shortly after birth ...	?	shortly after birth
Rapid increase of intensity of the icterus	+	+
Other cases in family, or of hydrops foetalis or of congenital anaemia	−	−
Drowsiness during the period of severe icterus ...	+	+
Pale stools	+	slightly
Bilirubinuria	+	−
Bilirubinaemia	+	+
Van den Bergh test in serum, mostly directly or indirect	+	+
Liver enlarged	slightly	slightly
Spleen at least temporarily much enlarged	−	−
Anaemia (often hyperchromic)	−	slight
Purpura	−	slight (?)
Erythroblastaemia during first days of life	−	−
Megalocytosis with increase of mean diameter, especially during the first week of life	−	−
Decrease in mean diameter in later stage	+	+
Thrombocytes decreased	−	−
Reticulocytes increased	−	−
Toxic blood picture	+	+
Symptoms of nuclear jaundice	+	+

* Of course this increase was observed in cases of icterus gravis neonatorum in which there was erythroblastaemia. Whether it would be present in those rare cases of icterus gravis neonatorum without erythroblastaemia or not has never yet been studied.

(e) In some cases recovery from icterus gravis neonatorum may be accompanied by cirrhotic changes in the liver. During life both of the present infants showed some signs of a parenchymatous liver affection (increase of the globulin content of the serum in both cases, with positive Takata-Ara test and increased sedimentation rate in the defibrinated blood in case 1), which corresponded in case 1 with a slight hepatic fibrosis found at the autopsy.

(f) Demyelinization and loss of ganglion cells in the globus pallidus and in the corpus subthalamicum on both sides (only in one of the two cases a slight icteric staining of the basal ganglia macroscopically was still visible at the autopsy; this causes no surprise as both infants remained alive for a long time after the jaundice had disappeared.)

II. As regards the cause of nuclear jaundice in icterus gravis neonatorum different opinions have been given in the course of years. A survey of these theories may be found, e.g., in the recent article of Zimmermann and Yannet. The present cases give further information on the histo-pathological side of this problem as the preparations only show the residual effect (demyelinization and loss of cells) and the bile pigment originally present has completely or almost completely disappeared. It can only be said that these cases prove that nuclear jaundice is not definitely related to icterus gravis neonatorum, but may also occur in septic jaundice of the new born.

III. From the literature (e.g. from the data of Schmorl who only found six cases of nuclear jaundice in 120 icteric new-born infants, making no distinction between familial and septic forms) it must be concluded that nuclear jaundice is very frequent in icterus gravis neonatorum, but on the contrary is exceptional in neonatal sepsis with jaundice. To explain this fact the symptoms of hypoplasia of the corpus callosum and fornices seen in both these cases, may be noted. These must be explained as a disturbance in development. It is a well-known fact that in brains which show disturbances in development the function of the barrier between blood and cerebrospinal fluid is insufficient. Perhaps this may explain why in these cases a nuclear jaundice developed. A similar state of affairs is seen in the frequent occurrence of encephalitis in infants with a congenitally malformed brain.

Summary

The clinical and pathological description of two cases of septic jaundice of the new-born (umbilical infection) combined with nuclear jaundice, giving rise to an extrapyramidal neurological syndrome, is recorded.

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CASE REPORTS

THREE CASES OF NON-BACTERIAL MENINGITIS

BY

J. A. CARDNO, M.B., CH.B.

Although many cases of acute aseptic or non-bacterial meningitis have now been described the etiology of the condition remains obscure. The following three cases have been observed during the last eighteen months. In all three the cerebro-spinal fluid remained sterile on culture and no organisms were seen in the direct films. In none of the cases was there any suggestion of middle-ear disease or sinus infection which might have caused a serous meningitis. All three made a complete recovery. It is suggested that the second and third cases may bear a different etiological interpretation from the first case.

Case records

Case 1. A female child aged four years was admitted to hospital on 24.8.35 with a history of having been off colour for four days. Vomiting had occurred on the first day and since then she had been lackadaisical and drowsy. On examination it was found that the child was drowsy, had a peevish cry and showed a disinclination to raise herself from the supine posture. All the tendon reflexes were diminished, the abdominal reflexes were not elicited and the plantar responses were flexor.

The following day there was some neck rigidity and slight spasm of the hamstring muscles. Lumbar puncture yielded clear fluid under pressure which showed an increase in cells and protein and a diminution in chlorides. The following day neck rigidity was marked and Kernig's and Brudzinski's signs positive. These meningitic signs persisted until 11.9.35, becoming less definite as time went on. Throughout the child was afebrile apart from an occasional rise of temperature to 99° F. which could be attributed to severe constipation.

The changes in the cerebro-spinal fluid are shown in table 1 A.

Case 2. A female child aged two years was admitted to hospital on 13.12.36 with a history of having been ' miserable, listless and crying for two days.' She had been holding her head a good deal and seemed to like resting it on a chair or bed. On the day of admission she had been vomiting

everything. For half an hour prior to admission the left side of her face had been twitching. Examined on admission the child was seen to be very ill and was having Jacksonian convulsions affecting the left side of the face, left leg and left arm.

Lumbar puncture, performed immediately, yielded a clear fluid under slight pressure. About 15 c.c. were run off after which the convulsions gradually became weaker, more discrete and finally ceased. The temperature on admission was 99·4° F., the pulse 150. On 14.12.36 the child was quiet, listless and pale. Two minor fits had occurred during the night. The temperature was 100·8° F., pulse 140 and respiration rate 24. Apart from slight neck rigidity there were no signs in the central nervous system. The report on the cerebro-spinal fluid showed a high proportion of lymphocytes, an increase in protein and a low chloride content. On these grounds a tentative diagnosis of tuberculous meningitis was made with a grave prognosis.

During the succeeding four days the signs of meningitis become more definite. The temperature remained above 99° F., the child resented being touched, neck rigidity became marked and Kernig's and Brudzinski's signs were positive. A second lumbar puncture on 18.12.36 showed a decrease in cells and a return to normal on the part of the chlorides. Thereafter the clinical condition began to improve slowly, temperature fell to normal, the child became a little brighter and her appetite improved. The changes in the cerebro-spinal fluid are shown in table 1 B. Meningitic signs persisted until 10.1.37, or four weeks after admission during which time she continued to have slight elevations of temperature. Throughout this period her mentality was remarkably dull for a child of her age. She did not attempt to speak at all and appeared to require re-education in simple actions such as feeding herself, playing with toys, etc. For several days she had to be told who her parents were as she failed to recognize them.

Case 3. A girl aged thirteen years was admitted to hospital on 8.1.37 with a history of headache and an attack of shivering on the previous afternoon. She had vomited the preceding night and twice on the day of admission. For three hours before admission she had been feverish and delirious. Examined on admission she was found to be very ill, pale and drowsy. The temperature was 99° F., pulse 100 and respiration rate 18. The only positive signs on examination were slight, generalized abdominal tenderness, marked neck rigidity and positive Kernig's and Brudzinski's signs. Lumbar puncture was performed forthwith and the cerebro-spinal fluid was found to be turbid and under pressure. On 9.1.37 the child seemed brighter and the meningitic signs, although still present, were less marked. As the first specimen of fluid had shown masses of polymorphonuclear cells, increased protein content and absence of sugar, a tentative diagnosis of meningococcal meningitis was made, although no organisms had been seen. Accordingly a further 20 c.c. of turbid cerebro-spinal fluid under pressure were run off and 15 c.c. of anti-meningococcus serum administered intrathecally while 10 c.c. were injected intramuscularly. This procedure was repeated on 11.1.37 and had the effect of producing a severe serum rash two days later, but could not be considered otherwise to have affected the course of the disease. Subsequent changes in the cerebro-spinal fluid are shown in table 1 C. The temperature fell by lysis, reaching normal on 17.1.37. The meningitic signs cleared gradually, having all disappeared by 22.1.37, exactly two weeks from the onset of the illness.

TABLE I.

	Date	Pressure	Colour	Cells per c.mm.	Polymorphs per cent.	Lymphocytes per cent.	Protein mgm. per cent.	Globulin	Sugar mgm. per cent.	Chlorides mgm. per. cent.
A	27.8.35	+	Clear	15	0	100	80	+	58	680
	29.8.35	+	Opaque	230	5	95	100	+	61	660
	5.9.35	±	Clear	20	5	95	100	±	60	706
	9.9.35	Not +	Clear	4	0	100	50	+	70	706
B	13.12.36	+	Clear	87	14	86	40	0	95	680
	18.12.36	+	Clear	70	2	98	60	+	91	720
	5.1.37	Not +	Tinged with blood. (Traumatic)	16	10	90	50	+	50	766
C	8.1.37	+	Turbid	masses of polymorphs			250	++	0	648
	12.1.37	+	Opaque	400	95	5	45	+	55	720
	15.1.37	240 mm. of water	Clear	68	85	15	30	±	54	700
	23.1.37	170 mm. of water	Clear	6	0	100	20	0	74	780

Discussion

Case 1 occurring in the late summer, is fairly typical of acute aseptic meningitis as described by several observers. In case 2, while the cell picture is fairly typical of acute aseptic meningitis, the onset with Jacksonian convulsions is uncommon, although some cases with convulsions have been described in very young children. The mental apathy after the acute stage of the illness had subsided, and the apparent amnesia for simple actions recently learned are also unusual, and somewhat suggestive of an encephalitis, although eventually they cleared up completely. The interesting feature of case 3 is the high original protein content of the cerebro-spinal fluid and the persistent preponderance of polymorphonuclear cells. Several cases have been described in which the cells were at first chiefly polymorphs and later replaced by lymphocytes, but this change usually occurs at an early stage of the disease. In this case the illness had practically run its course before any change took place. In both the second and third cases the onset was more sudden and severe than in the first case and the children were more seriously ill during the first few days. The meningitic signs and cytological changes also persisted for rather longer than is usual in acute

aseptic meningitis. The first case occurred in the summer the second and third in mid-winter at the height of an influenzal epidemic. At this time scores of other children from the same district were seen with influenzal broncho-pneumonia and the appearance of these two cases at such a time suggests that they were possibly neurotropic or meningotropic manifestations of the influenza virus. It would be interesting to know if other cases of a similar nature were observed at this time.

I am indebted to Dr. W. Pickup Greenwood, Medical Superintendent, Bethnal Green Hospital, for permission to publish these cases.

PRIMARY TUBERCULOSIS OF THE SKIN

BY

O. S. ROUGICHITCH, M.D.

(From the Department of Paediatrics, University of Belgrade, and the Infant's Home 'Dom Materinskog Udruzenja' in Belgrade.)

Medical literature contains many reports of cases of primary tuberculosis of the skin. The majority of these, however, deal either with examples of primary tuberculosis following circumcision or with the cutaneous lesions which occasionally may be produced by the injection of B.C.G. vaccine. A few years ago W. Krantz[1], while making an extensive review of this subject, was able to collect from the literature about fifteen cases of positive primary tuberculous involvement of the skin with histological and bacteriological evidence. In 1936 Kereszturi and Siegal[2] recorded two personal observations which were probably instances of primary tuberculosis of the skin, and at the same time they quoted eleven additional examples of primary tuberculosis of the skin with histological proof which had been published since the appearance of Krantz's communication. As the condition would therefore seem to be relatively uncommon the following observation is of interest.

Case record

M. T., a female infant, born of unknown parents, was found on July 31, 1936, in a suburb of Belgrade, and sent to an institution for sick children, where she was kept for nearly two months. She was then discharged from that institution and admitted to the Dom Materinskog Udruzenja. The papers accompanying the child supplied the following information:—'A healthy infant, artificially fed, gain in weight steady and satisfactory. On admission was given injection of B.C.G. The cutaneous and the intracutaneous tuberculin tests are negative.' On coming under my care the infant was about ten weeks old. Weight 4·25 kgm., height 56 cm. She was somewhat pale and moderately undernourished. Pirquet test was performed immediately after admission and was found to be positive. During the first week of residence the infant developed a bilateral otitis media with high fever and severe constitutional symptoms. Both ear drums were incised and in a few days the temperature returned to normal.

On the day of admission to the Dom Materinskog Udruzenja a small brownish red circular crust, about 0·75 cm. in diameter, was noted in the right mammary region (fig. 1). The immediate surroundings of the crust were somewhat infiltrated, and the edges unusually hard. When the crust was removed a bluish red surface, with a central necrotic ulcer was

disclosed. The corresponding regional lymph glands in the right axilla were considerably enlarged and fluctuating, but the skin in this situation was normal. Two weeks later puncture of the glands revealed thick yellowish pus, smears of which were positive for tubercle bacilli. The puncture was followed by a fistula, which is still discharging thick yellowish pus. From that time the temperature started to be irregular, ranging between 37·5° and 38° C. Otherwise the infant looked well and thriving and had made a gain in weight of 3·75 kgm. in four months. Skiagrams, according to Dr. W. Alberti, show 'no evidence of enlarged glands or tuberculosis in the thorax.'

A biopsy of the cutaneous lesion was carried out by Dr. D. Tichomiroff, who reported as follows:—

'The biopsy specimen from the cutaneous lesion was a piece of hard, reddish brown skin tissue, 0·7 by 0·8 cm. The superficial squamous epithelium shows moderate keratinization and its basal layers contain less melanin than normally. The connective tissue is almost completely diffusely

FIG. 1.—Showing the primary complex of the skin.

replaced by a non-specific granulation tissue, which is fairly well infiltrated by lymphocytes and plasma cells. Immediately beneath the epithelial layers, in the connective cutaneous tissue, there are occasional groups of giant cells, which are surrounded by small collections of epithelioid cells. In one such collection there is a large focus consisting of a great number of small tuberculous nodules. This focus contains a large number of lymphocytes, plasma cells, epithelioid cells and occasional giant cells (fig. 2). Some small groups of these cells are very faintly coloured (caseous necrosis). The whole focus is poorly vascularized. In the subcutaneous tissue there are groups of small solitary tuberculous nodules showing initial and central caseous necrosis.'

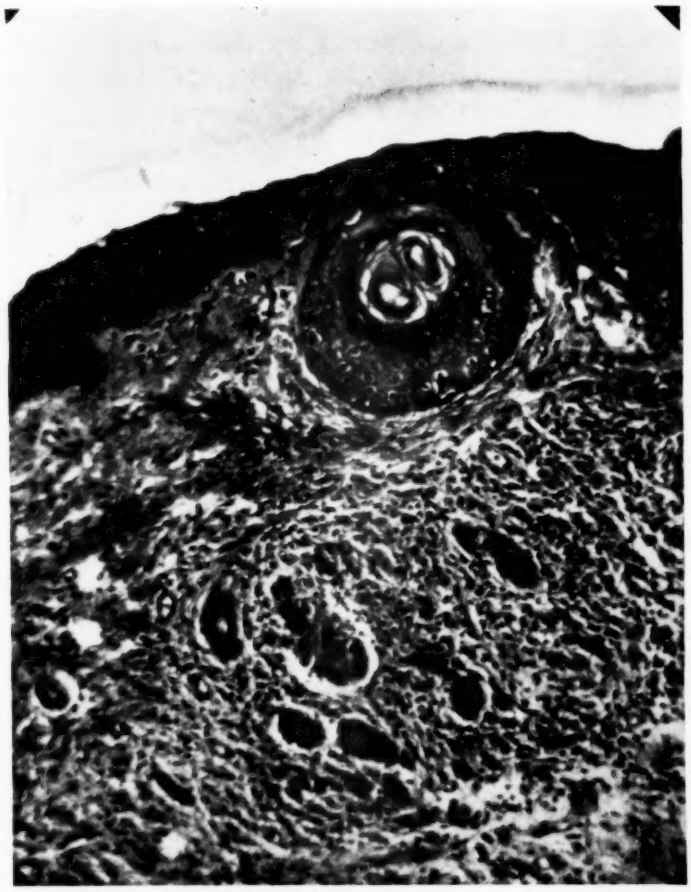

FIG. 2.—Microphotograph of skin lesion showing a group of tuberculous nodules and giant cells immediately beneath the skin epithelium, × 160.

Comment

The above case may be considered an example of primary tuberculosis of the skin. That the condition was tuberculous is shown by the histological and bacteriological findings, and it is on the following grounds that the lesion in the mammary region has been regarded as the primary focus:

(a) The absence of evidence of previous clinical tuberculosis.

(b) The slow and torpid evolution of the cutaneous lesion, and the degree of involvement of the corresponding lymph glands with their rapid liquefaction.

(c) The negative reaction to the cutaneous and intracutaneous tests until the age of two and a half months, i.e., until the primary complex was recognized.

(d) The age of the patient.

As to the method of infection there are two possible explanations. The localization of the lesion suggests that the infant had probably suffered from the so-called genital crisis of the breast, and that the ' witch milk ' had been suckled (a custom which is quite common in some parts of this country) by a tuberculous individual. Or perhaps the infant had some kind of lesion of the skin which subsequently became inoculated in some other way with tubercle bacilli.

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PELLAGRA IN AFRICAN CHILDREN

BY

H. C. TROWELL, M.D., M.R.C.P.,
Medical Officer, Uganda Medical Service.

Definition

Pellagra in African children and infants displays certain unusual features. It is an endemic disease which has been described in certain African tribes both on the East and West Coast and also in Central Africa. It is characterized by an acute course progressing usually towards a fatal termination in the second and third month. It displays itself by oedema which is often severe, a rash which in some respects is unlike the classical description of that in pellagrous adults, diarrhoea, dysentery and perhaps fatty stools. Only a few cases develop obvious neurological signs. Differing thus from the more common but slow and remittent type of the disease as seen in adults no clinical observer who has recorded cases in Africa has been able to agree that it is pellagra. Its interest for English clinicians lies in the points in which it resembles and yet differs from pink disease. It is known variously in Africa as ' Gillan's oedema,' ' Williams's disease,' ' malnutritional oedema,' and is believed to be a new clinical entity.

General considerations

It is not suggested in this article that the disease is anything but pellagra. Nevertheless until this opinion has proved acceptable it may be as well to designate it ' infantile pellagra ' since slow and remittent pellagra which conforms with the usual descriptions has been described in children (Goldberger and Wheeler[12]). The addition of any terminology to a subject as large as pellagra is regrettable, but this variety displays certain unusual features, notably oedema, which is sometimes extensive, pallor of the negroid skin, and fatty stools which cannot easily in the present state of knowledge be related to the usual clinical findings in pellagra.

Further support for a possible variation of the clinical picture of pellagra when found in African children may be gained from a consideration of the fact that other known deficiency states display a different clinical picture in children and adults. Scurvy was first known in adults; then Barlow gave his classical description of the disease in infants. Beri-beri was first known in adults; more recently Bray[2] has given a description of the infantile variety. Rickets and osteo-malacia stand largely to one another as the same deficiency in children and adults. If pellagra occurs in infants it would be surprising if it reproduced exactly the same clinical condition as found in adults.

Historical

Infantile pellagra has been described by various observers in East and West Africa who believed that they were dealing with a new clinical entity, and rejected the idea that the disease was a manifestation of pellagra.

Sequeira[27] has recently drawn attention to the fact that the first brief clinical description was given by Procter[25] while working in the Kikuyu reserve of Kenya Colony:—

'The other disease occurs only in quite young children, the child is nearly always an extraordinary light colour and is usually brought up on account of swelling of the feet. The only history obtainable appears to be that in a number of cases there had been slimy motions for some time. As the disease progresses the child becomes paler in colour and the pigment seems to be concentrated into a curious black desquamation which is most often seen at the bends of the elbows and knees, and there may be a general oedema. The child, so far as my information goes, nearly always dies.'

Williams[35] then recorded her observations in the Gold Coast, reporting some twenty cases, with three post-mortem examinations. She gave a good description of the skin changes and the oedema. The gastro-intestinal signs were also noted, but the stools, which were not analyzed, did not appear fatty. No neurological changes apart from irritability were noted by her. A nutritional deficiency was postulated and in her opinion the distribution of the rash precluded the possibility of pellagra.

Gillan[10] unaware of these articles described twelve cases of a mysterious form of fatal oedema attacking infants in the Kikuyu country near Nairobi, Kenya Colony. He noted the skin changes and proved the high fatty content of the stool in one case. Bacilluria was present in two cases. Two post-mortem examinations were performed, but apart from a fatty liver nothing else was noted. The blood changes were described by him and were recorded in six patients, three of whom had a hypochromic anaemia and three a hyperchromic anaemia. In his opinion the disease was a new clinical entity and he considered its relationship to coeliac disease, sprue and pancreatic disease and also saw close clinical analogies to pink disease.

Meanwhile Stannus[30] reviewed at length the cases described by Williams, and to him belongs the credit of stressing the fact that the skin eruption was certainly typical of pellagra in native children.* Williams[36] published a second article which drew from Stannus[31] even more stringent criticisms. Stones[37] and Carman[3] recorded cases in Uganda and Kenya of 'Gillan's oedema' for they were unable to accept the attention drawn by Loewenthal[17] to the opinion of Stannus[30]. Dyce Sharp[28] recorded another case on the West Coast. Much confusion has therefore arisen in the tropics where 'Gillan's oedema' and 'malnutritional oedema' are described on the East Coast and finally 'Williams's disease' and 'Kwashiorkor' in West Africa.

Finally, a long review was published by Stannus[32] of these cases. He was then of the opinion that Gillan's cases 'would appear to be more closely allied to child beri-beri.' The writer has visited the hospital where Gillan worked; it is close to the place where these observations were made and it is certain that the disease is the same at both places.

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* After seeing the photographs published with this article, Stannus is further confirmed in this opinion.

The present series of observations

1. Locality, distribution, age and sex.—Observations were made on twenty-six patients who were admitted to Nairobi Hospital, Kenya Colony, during 1934 and 1935. In addition, in neighbouring hospitals of Kikuyu country some twenty other cases have been observed by the writer but are not included in this series. All were African children. Such children come to Nairobi Hospital largely from the surrounding Kikuyu reserve and to less extent from the less numerous and more scattered Masai and Kamba tribes. Immigrant labour in Nairobi township, mainly Luo, is also the source of nearly half of the routine admissions to the children's ward, and resident Swahili families in the native locations of Nairobi normally contribute a few in-patients. Nevertheless, the disease shows a definite selection of the Kikuyu tribe (24 cases); there was only one case from both the Luo and Swahili tribes. This is consistent with a disease due to a dietetic deficiency.

Infantile pellagra occurred only in children from six months to four years of age. The age incidence was as follows:—6 months—1 case, about 1 year —3 cases, about 2 years—12 cases, about 3 years—5 cases, about 4 years—5 cases. Two typical cases of the usual type of pellagra were seen by the writer in older Kikuyu children aged 9 and 12 years respectively. Both had scaly dermatitis on the lower arms and legs, relapsing diarrhoea and signs of involvement of the pyramidal tract. One had slight oedema of the ankles and proceeded to dementia and death. Pellagra, however, is at present almost unknown in the native adult community and Dr. H. L. Gordon, Visiting Physician to Mathari Mental Hospital, Nairobi, in a private verbal communication, stated he had never seen a case of dementia due to pellagra.

Stannus[32] has reviewed at length the published reports on pellagra on the East and West Coast. Briefly, apart from pellagra in institutions, such as jails, few cases have been reported, but it is suggested in this review that this disease may be much more common than might be expected, since it may easily be overlooked by those who are unacquainted with the protean manifestations of the disease. The writer, however, has not yet seen pellagra in an adult of Kenya or Uganda. The series comprised 14 males and 12 females.

2. Seasonal distribution.—The first signs of illness appeared with equal distribution during all months of the year with the exception of July and August, when no cases occurred. These months have the least amount of sunshine, for the sky is usually completely clouded over. Other months have several hours of sunshine each day. The hottest season is from January to March. During the rains which occur mainly in November, April and May there is much sunshine between the heavy showers. It has been stated that in temperate regions pellagra is found more during the spring months. In the tropics there appears to be no seasonal variation and in a series as small as this the absence of new cases in the cloudy months of July and August may be only fortuitous.

3. The clinical picture.—(a) THE ONSET. Patients presented themselves on an average about a month after the alleged onset of the complaint, but careful questioning revealed the fact that the child had been ailing for some time before the occurrence of definite illness had been recognized. During this preliminary period the child had appeared wretched, had shown irritability, photophobia, a desire to sit down rather than to run and play, some anorexia and perhaps some puffiness of the face, hands and feet. These preliminary signs may simulate pink disease, a point which is discussed later.

After this preliminary period the occurrence of any one or all of the main signs of the disease; oedema, the rash or gastro-intestinal symptoms ushered in unmistakable signs of illness. Of these oedema was usually the first to appear but any one of these three conditions may precede by a week or two, but seldom longer, the appearance of one or both of the other signs.

FIG. 1.—Infantile pellagra, showing large areas of the exanthem.

(b) OEDEMA. The oedema was stated to have begun abruptly in the majority of cases and to have proceeded to its greatest extent in a few days. It might be slight and in two cases it was absent throughout the entire illness. In the majority it soon became moderate, in a minority it became extreme. When slight it was limited to the face, hands and feet. When severe it was generalized; the face resembled that of a patient with acute nephritis and the eyes were often completely closed. Serous sacs were also involved. The severe oedema was usually more in the dependent parts so that on waking in the morning a child who had slept on one side might have the lower eye completely occluded. In rapidly progressive cases death intervened in the oedematous stage, in less rapid cases the oedema showed a tendency to abate or even to disappear before death, recovery, or an intermediate state of partial recovery ended the period of observation in the hospital. As the oedema disappeared great emaciation was noted in un-

favourable cases and it was as emaciated infants but showing little or no oedema that bodies came most frequently to post-mortem.

(c) THE EXANTHEM. This was present in all except one early case, which presented only oedema and gastro-intestinal signs. Many cases, however, occur of children who have oedema and some gastro-intestinal upset but in the present state of knowledge it would be unwise to include them. Doubtless some are cases of infantile pellagra, but until more is known of this condition, there would be a tendency to include other diseases such as errors of feeding, cachectic oedemas, nutritional oedemas, anaemic

FIG. 2.—Showing oedema, 'crazy pavement' black patches and pale areas, and generalized pallor of the skin except at the black patches.

oedemas, among those who certainly have all the stigmata of infantile pellagra. The skin changes were extremely complex but they may be discussed under the various heads, and indeed in many cases there appears to be a definite sequence of evolution. This cannot be demonstrated in the majority of cases.

(i) Black patches occurred as jet-black areas of hyperkeratosis. They were slightly raised above the surface of the surrounding skin, but this was never obvious except to the closest inspection. They never resembled the

raised kerato-follicular lesions of Majoochi which are a classical variety of the pellagrous rash, nor the enlarged sebaceous glands of Nicholls[22], nor the pilo-sebaceous folliculitis of Loewenthal[16], all of which are in the opinion of Stannus[32] probably identical, and are manifestations of pellagra. Black patches were the commonest early characteristic lesion. They varied in size from an eighth of an inch to that of one continuous plaque covering most of the abdominal wall. The patches often extended in area until they became confluent and it is assumed that the large plaques arose in this

FIG. 3.—Showing alopecia, pale hair, pale areas, septic skin lesions.

manner. The patches showed a tendency to exfoliate disclosing underneath areas of pink or pale skin. They had usually a smooth shining flat surface as if black varnish had been painted on to the skin and had subsequently cracked. They thus resemble the pellagrous exanthem as described by Stannus[29] in Nyasaland.

(ii) Pale areas varied in shade and colour being dead white, coffee-coloured, pink or copper-coloured. In many cases they were found where it could be presumed that black patches had peeled, or septic skin lesions had occurred, but it was not by any means certain that all pale areas had arisen in this manner. Pale areas were commonest where a discharge had favoured early exfoliation of the black patch, that is around the mouth, nose, anus and penis and also in the moistened groins and armpits.

(iii) Sodden areas of heaped-up white skin or of raw excoriated skin were seen at the lateral corners of the mouth, around the nostrils and canthi of the eyes, and around the anus. The prepuce was frequently ulcerated either at its free surface or on its inner surface. The labia majora were often completely raw and sodden. The scrotum showed raw excoriated areas.

(iv) Fissures occurred at the natural flexures of the skin but only in the later stages of severe cases. Deep linear fissures, invading the subcutaneous layer and showing no surrounding inflammatory reaction or discharge were seen in the groin, in front of the elbow, above and around the anus, at the lateral corners of the mouth, at any part of the lips, at the corner of the nostrils and above and below the pinna.

(v) Generalized hypo-pigmentation of the skin occurred in most cases in addition to the localized hypo-pigmentation of the pale areas. In the majority, but by no means in all, the whole of the body became pale, so much so that the children might be a pale coffee-colour and could be diagnosed correctly even when seen a long way off. On entering a ward full of black babies these coffee-coloured patients attracted so much attention that from this alone it was possible to diagnose infantile pellagra. It is quite true as Williams[35] has stated that all African patients who suffer from any cachexia show generalized loss of skin pigment, but this change is seldom a marked one. In infantile pellagra the loss of pigment is usually more marked than in any other disease, and is therefore in the opinion of the writer probably a specific change and not merely a manifestation of cachexia. In patients who are recovering the pigment re-appears.

(vi) The hair and nails showed changes. In the former they were so marked that they must be considered specific; in the latter the changes are found in other conditions of cachexia. There was a marked loss of hair. In some cases almost complete alopecia was found and the remaining hair was all shades of chocolate, coffee, or even grey and white; it was also thin, brittle and straight. Normal African hair is coarse, tough, extremely curly and jet black. In conditions of cachexia the African hair tends to become straighter and paler but the changes are not as marked as in infantile pellagra. The nails were often as thin and soft as paper and exhibited longitudinal ridging. The hair changes have been noted in pellagra and have been produced in experimental animals suffering from a deficiency of vitamin B_2 by Goldberger and Lillie[11].

(vii) Septic skin rashes of all varieties such as impetigo, bullous impetigo, pustules, and boils were common.

The character of the rash was modified by the oedema for the black patches, especially if large, did not allow distension to occur. The normal furrows of the skin appeared as pale shallow cracks leaving the black patch as ' crazy pavement,' an excellent description of Williams[33]. In early cases the skin all over the body appeared slightly rough and branny desquamation occurred. The skin had an atrophic shining appearance. These early changes have been described in pellagra, but by themselves are not in the opinion of the writer sufficiently distinctive to be included under the specific changes seen in African infants. The distribution of the rash, as Stannus[30] has pointed out, must be regarded as suggestive of pellagra although it does not conform to the usual description as given in text-books, and for this reason neither Procter, Williams or Gillan considered it pellagrous. In adults pellagra usually appears as an insidious disease and the rash appears as successive crops of dermatitis on the exposed surfaces of the nape of the neck, the bridge of the nose and the backs of the hands. These are the parts irritated by trauma, wind, dust and sunlight and Stannus[32] has drawn attention to the fact that it cannot be adequately explained in terms of solar irradiation. Undue attention has been paid to this in the usual text-book descriptions, but it cannot be stressed too much that the rash appears in areas subject to all forms of irritation. In any case the pellagrous rash in semi-naked African children might be expected to differ from that in clothed Europeans, whose skins are not protected from sun trauma by the deep pigment present in the native skin.

The rash occurred principally on the areas exposed to the irritation of pressure or of some discharge and bore no relationship to the parts exposed to solar irritation. Pressure produced the rash over the buttocks, back of the thighs, and the calves of a sitting child, and in addition over the back of the trunk, the great trochanter, the back of the shoulders and arms especially at the elbows of a recumbent child. The scrotum was commonly affected and appeared to itch for scratching was frequent. Clothing was variable in nature and extent so that its rubbing had usually produced changes over the napkin area, outer sides of the thighs and knees. The irritation of discharges had produced the rash in the perineum (due to diarrhoea) and around the mouth (from increased salivation) and nostrils (from the nasal discharges). This was the essential distribution of the rash in most cases. Severe cases may show the rash in all parts of the body, but in every case the changes were maximal over the buttocks and perineum. Solar irritation had in a few cases produced the typical pellagrous scaly dermatitis on the backs of the forearm and the dorsum of the foot and the crown of the head. In one case this rash ended dramatically where a short sleeved shirt finished in the upper arm. In most cases the skin appeared extremely irritable and scratching was excessive. This may explain the frequent occurrence of septic skin rashes which complicated the clinical picture.

(d) Gastro-intestinal signs. Loss of appetite was frequently severe. The children often refused everything but the nipple, which was continuously sucked by day and by night. Other children sucked fingers or clothes and made continuous champing movements with the jaws. Vomiting was not common except at the outset. In a few cases the tongue was furred and raw at the edges but usually it was smooth, denuded and contained no fur at all. Aphthous stomatitis was present in a few cases. Salivation appeared excessive. It is impossible to state if soreness of the mouth, so suggestive of pellagra, was present, but it may be presumed from the difficulty in feeding the child with anything but liquid food. All except four cases gave a history of loose stools and subsequently developed these while in hospital. There were spontaneous remissions and exacerbations of this intestinal upset. During the exacerbations blood was frequently seen in the stool, in two cases blood and mucus were passed, but as subsequently stated no cause was found for this dysentery. During less severe exacerbations diarrhoeic stools of all varieties of consistency and colour were seen. Fatal cases often had persistent diarrhoea.

When the gastro-intestinal symptoms were not severe the majority of patients passed a stool which has been accurately described by Gillan[10]. It was pale, soapy, soft and bulky and had a peculiar offensive odour. Undigested food could frequently be recognized by the naked-eye. As discussed later it was found by analysis that fat was present in this stool in large amounts. This type of stool improved under treatment in favourable cases.

(e) Neurological symptoms and signs. The onset was marked by wretchedness and irritability. The children refused to play and sat sadly, then took to bed. In bed they lay curled up and covered by bed-clothes. Photophobia and red eyes were often present. Children were petulant, were continually crying, were suckled continuously by indulgent mothers, hanging almost by the hour from the nipple. Others sucked fingers or a thumb. Some indulged in excessive scratching which was unexplained by any known cause. They presented a constant picture of misery. In these mild cases the only neurological sign found in the majority, but by no means all, was marked hypotonia of the muscles. The fingers could commonly be bent backwards until they lay parallel to the forearm and the whole foot could be dorsiflexed to an angle of forty-five degrees with the lower leg. Limbs could be twisted into unnatural positions. In these cases no alteration was detected in power, sensibility to pain or in the tendon reflexes. The majority died in this condition with no other sign of nerve involvement and the majority who recovered showed nothing else.

In eight patients, however, the picture of hypotonia and the absence of other neurological signs gave place to the picture of hypertonia, increased tendon reflexes and an extensor plantar response. The first indication of this change was an increase of tone most marked in the legs which were adducted and flexed at the hips. Later the arms were held rigidly in general flexion. Tremors were noted in a few of these cases in the arms and the

legs, but never in the tongue. The tendon reflexes became unduly brisk but ankle-clonus was never definite. In three cases both plantar responses became definitely extensor at an age when the normal response should be flexor. The abdominal reflexes were never lost. No cranial nerve involvement was detected, but the optic disc was seldom examined. Muscular cramps were common in the legs of these advanced cases.

Changes in the special senses were limited to the eyes where conjunctival injection and increased lachrymation were common. Mild conjunctivitis and blepharitis were common. As a food deficiency had been postulated every case was examined for xerophthalmia but this was only found in one case as a terminal condition.

Drowsiness, so typical of pellagra, was frequently seen in the last few days of life. Dementia was never seen but its recognition in young native children is extremely difficult and would not be expected in these acute cases.

(f) URINARY SIGNS. A faint trace of albumin was detected by the boiling test in eight cases. This could be explained by urinary infection, fever, toxaemia and cachexia; and albuminuria is seen in pellagra. Williams[35] and Gillan[10] detected no albumin in their cases so that in their opinion this formed the main distinction from nephritic oedema. In the opinion of the writer nephritis is excluded by the absence of other signs of nephritis and the presence of other signs of infantile pellagra, notably the rash. Maclean's urea concentration test was performed in these eight cases of albuminuria and gave normal concentrations except in one infant who could not be separated from the mother. She suckled it continuously and diuresis may thus explain the low concentration of 0·9 per cent. urea in the urine. Nephritis was not detected at post-mortem examination. Bacilluria was common and B. coli were cultured in large numbers from the catheter specimens of five cases. Pyuria was detected in three of these specimens.

(g) RESPIRATORY SIGNS. A persistent purulent nasal discharge was often present. A few cases showed signs of bronchitis and a terminal but silent bronchopneumonia was one of the commonest causes of death, being found in half of the cases.

(h) CARDIO-VASCULAR SIGNS. In most severe cases the extremities were unduly cold and clammy, but apart from this no increase of sweating was noted. The pulse-rate was usually quickened but could adequately be accounted for by fever or cachexia. Apart from a terminal heart failure from the same causes, no signs of heart failure were found to explain the oedema or to suggest that the disease was a manifestation of beri-beri.

(i) GENERAL SIGNS. Severe emaciation disclosed itself in unfavourable cases as soon as the oedema disappeared. In less severe cases no increase of weight, that is no growth occurred, until all the other signs of the illness had disappeared. Fever of an irregular type was present in most severe cases, during some period or other of the complaint. In mild cases or those

undergoing recovery the fever was mild or absent, in fatal cases the temperature rose higher. In most cases adequate cause of the fever could be detected in septic skin affections, pyuria, enteritis, bronchitis or bronchopneumonia. Pallor of the mucous membranes was present in severe cases of anaemia.

Investigations

1. Investigations yielding negative or inconclusive results.—Blood films were examined in every case and revealed sub-tertian parasites in four cases due to a superimposed malarial infection. The Kahn test was performed on all infants and their mothers; all the former gave negative results, five of the mothers gave a feeble positive reaction, presumably due to old yaws which was formerly common among the Kikuyu, among whom syphilis is rare. There is thus no evidence that the disease is a manifestation of congenital syphilis as some have suggested and for which the majority have in the past been treated.

The stool was examined twice for ova and cysts and a culture (when possible employing the faecal mucus) was performed on every case. Culture revealed only B. coli except in one case in which Morgan's No. 1 bacillus was found. Stools were examined for ova and cysts after spinning with saline and examining the deposit. The following ova and cysts were seen:—Taenia saginata two cases, Ankylostoma duodenale four cases, Ascaris lumbricoides three cases, Trichuris trichiura one case, Giardia intestinalis four cases, Chilomastix mesnili one case, Strongyloides stercoralis two cases, Entamoeba coli five cases, Oxyuris vermicularis one case. No known cause of dystentery or enteritis was found and the oedema cannot be explained by ankylostomiasis.

X-ray films were taken in one case and revealed no evidence of rickets nor were any signs of this disease obtained clinically. Dentition was normal.

2. Investigations yielding positive results.—TOTAL AND DIFFERENTIAL BLOOD COUNTS. These were performed on twenty-cases. Practically no case gave a normal blood picture Comparison had to be effected with European normals, since these figures for African children resident at Nairobi, a height of 5,000 feet, are not known. Seventeen cases showed varying degrees of microcytic anaemia. The haemoglobin estimated in fifteen cases by Sahli's method averaged 77 per cent. and ranged from 50 to 93 per cent. The red cell count averaged 3,900,000 and ranged from 2,740,000 to 5,290,000 per c.mm. The colour index averaged 0·78 and ranged from 0·57 to 0·98. The mean diameter of the red cells estimated by Eve's halometer averaged 7·64μ. In a few cases polychromasia and stippling were noted in the red cells; apart from this no other abnormality was seen.

Three cases showed a moderate macrocytic anaemia:—

Case 1: haemoglobin 70 per cent., R.B.C. 2,540,000, colour index 1·4, diameter of red cells 8·39μ. Case 2: haemoglobin 80 per cent., R.B.C. 3,600,000, colour index 1·2, diameter of red cells 8·00μ. Case 3: haemo-

globin 80 per cent., R.B.C. 3,700,000, colour index 1·1, diameter of red cells 8·00μ. In these three cases marked poikilocytosis, polychromasia and occasional normoblasts were seen. Megaloblasts were not seen. The first case had 1 per cent. reticulocytes prior to treatment and 8 per cent. a week after this had begun. The third case exhibited 20 per cent. reticulocytes a week after commencing dietetic treatment (marmite).

A slight degree of leucocytosis with a relative lymphocytosis was pesent in most cases. The white cell count averaged 13,200 and ranged from 8,400 to 23,000, a high count indicating infection.

The differential white cell count averaged:—polymorphonuclears 49 per cent., lymphocytes 41 per cent., mononuclears 7 per cent., eosinophils 3 per cent. No basophils were seen in any of the films. The Arneth index showed a shift to the left in the three cases in which it was estimated.

Stool fat content. Direct smears from the stools were made in every case. Undigested vegetable cells were present in a large number, so were fatty acid crystals and oil globules. Undigested meat fibres were not observed, but the diet contained only a very small amount of meat. Sixteen cases were examined for the fat content of the stool. They were unselected cases; death or early discharge prevented some patients from being examined. The results were expressed as percentages of the dried faeces and the figures were compared with those given by Cammidge. Seven of the sixteen cases fell within the normal range, the remaining nine cases gave abnormally high figures and are now given:—

	Cammidge's normal. per cent.	Average of 9 cases. per cent.	Range of 9 cases. per cent.
Total fat	15 – 25	42·9	33·0 – 57·4
Unsoaped fat	10 – 15	30·25	25·2 – 39·1
Combined fatty acid (soaps)	10 – 15	18·62	12·0 – 24·0
Free fatty acids	9 – 13	12·25	0·5 – 30·0
Neutral fat	1 – 2	9·14	2·0 – 24·6

In these nine cases there was a high fat content, nearly twice the normal figure being obtained. This was explained mostly by the high unsoaped fats and to a less extent by the high neutral fat content. Even in the six cases with a normal total fat content five had abnormally high neutral fat figures. There had been a considerable splitting of fat, but not as much as normally occurs since the neutral fats formed roughly a quarter of the total fat content as opposed to the normal ratio of one-tenth. In coeliac disease the splitting is adequate, so that the higher proportion of neutral fats in infantile pellagra than in coeliac disease forms an important distinction between the two diseases.

These findings in infantile pellagra indicate that there are two sources of failure in fat digestion; firstly, a slight failure to split fat (owing to a failure probably of pancreatic secretion), secondly, an even more marked failure to absorb such fat as is split (probably due to atrophic changes in the intestinal mucosa as will be demonstrated later). In coeliac disease there exists only the second factor.

Blood sugar estimation. Three cases were examined for the blood sugar variations after an amount of glucose proportional to the weight of the child had been administered. The following figures were obtained and are expressed as milligrams of glucose present in 100 c.c. of blood:—

Fasting level 72 mgm.; 30 minutes 130 mgm.; 60 minutes 137 mgm.; 90 minutes 80 mgm.; 120 minutes 67 mgm.

There was thus a low fasting level and a corresponding flatter type of curve. The number of cases is too few to allow the findings to be regarded as conclusive, but in this connexion the lower blood sugar curves may be compared to those found in coeliac disease, when there is also a failure of fat absorption (Fairley and Ross[7]).

Course and prognosis

Of the twenty-six patients nine died in hospital, five were discharged by impatient parents in an improved condition and ten were discharged free from all clinical signs of disease, and if any of these relapsed they did not report again to the hospital. The average period of stay in hospital of those who survived was about four weeks, after which it usually proved impossible to detain them or to secure their re-attendance. Patients who were rapidly cured presented themselves in the first week or two of the recognized illness; only two of those who were cured had been ill for as long as a month. These early cases responded fairly quickly but not dramatically to the treatment described later. When they were admitted the oedema was usually well marked, the skin changes were only slight, and no definite neurological changes, apart from hypotonia, were detected. Anaemia and fatty stools might be present. Diarrhoea was often present but responded slowly to the treatment. Fever was moderate and disappeared in every case that was improving.

Patients presenting themselves later than a month usually had severe signs. None of them was discharged cured; some were discharged improved after about another month's treatment; the remainder died. Only one of the fatal cases was presented for treatment after having been ill for less than a month. Fatal cases were often admitted moribund and died within a few days. Without the correct treatment the disease usually steadily advanced with occasional exacerbations to a fatal termination in the second or third month from inanition or earlier if bronchopneumonia occurred. Both Gillan and Williams recognized the fatal nature of the complaint.

Pathology

Six post-mortem examinations were performed, three by the writer and three by Dr. F. W. Vint, Government Pathologist, Medical Research Laboratory, Nairobi. The findings, apart from complications of broncho-pneumonia, urinary infection and the degree of intestinal congestion, were very consistent. The examinations were made on an average about twelve hours after death and for this reason the appearances recorded in the intestines must be taken with reserve.

Macroscopic changes.—These were obvious in the skin, thymus, liver and intestines. Normal appearances or only those of superimposed toxaemia and infection were present in the lungs, kidneys, spleen, heart, reproductive organs, brain and spinal cord. Subcutaneous fat was almost absent. Internal organs were pale if anaemia was present.

The thymus gland showed marked atrophy in all cases so that it was usually impossible to demonstrate it even after the most painstaking dissection. The liver was usually moderately enlarged and showed extreme fatty degeneration. Its surface and cut section were bright yellow, occasionally interspersed with small red areas of congestion. Its consistency was extremely soft except in cases in which a fine fibrosis was beginning to replace degenerate cells. The intestines had somewhat transparent thin walls and the mucous membrane appeared unduly smooth. This change was most marked in the small intestine but was present in all parts of the intestinal tract. Slight congestion but no ulceration was seen in the mucous membrane of the small and large intestine of those cases which had diarrhoea or dysentery. The suprarenal glands were moderately enlarged in size and weight and two cases showed haemorrhages in the cut section. The thyroid and pituitary glands appeared normal.

Microscopic appearances.—Most of the internal organs were studied in every case but unfortunately the central nervous system was never adequately examined nor was the skin. This is because the writer was investigating in East Africa cases of ' Gillan's oedema,' and only quite late in the investigation was his attention drawn to suggestions concerning its relationship to pellagra. Only then were neurological changes detected clinically and only then was the central nervous system examined microscopically. Only in the last two post-mortem examinations was the cervical cord, but no other part of the nervous system, sectioned and no abnormality was detected.

Toxic changes were evident in the tissues of many organs, cloudy swelling was usually marked in the kidney. Extreme fatty degeneration was present in the liver. In most cases the thymus had atrophied so much that it was impossible to identify the tissue, in a few cases in which it was recognized it showed great decrease of the lymphoid elements, but Hassal's corpuscles appeared normal. The suprarenal glands appeared normal in structure apart from the presence in two cases of haemorrhages in the zona reticularis of the cortex. The intestines revealed slight atrophy of the villi and mucous membrane and signs of congestion and inflammation in cases in which diarrhoea had been present. The skin revealed irregular changes according to the variety of the rash. There were areas of hyperkeratosis tending to separate from the corium. The papillary processes were shorter, had a less regular outline, and in some cases were markedly flattened. The pigment was distributed in an unequal manner, areas of hyperkeratosis containing excess, other areas of thinned atrophic skin where exfoliation had occurred revealing small patchy collections of pigment.

The pathological picture is therefore consistent with that of pellagra in negroes as described by Denton[5]. The atrophy of the thymus and the extreme fatty changes in the liver are anomalous features. The pathological picture is not proof of pellagra, since the distinctive changes in the gastro-intestinal tract and cental nervous system were not detected, for they were not searched for. The skin changes are however extremely suggestive.

The investigators had no experience of the pathological changes in pellagra were unable to find adequate descriptions in the literature available to them of the pathology of pellagra in the negro, and did not believe until the investigation was nearly completed that pellagra was a possibility.

Diet

It was impossible to gain from the mothers any adequate description of the diet of the child prior to the onset of the disease. This was not for want of prolonged questioning. It is unnecessary to give all the reasons for failure. Intelligent Kikuyu orderlies could detect no point in which the feeding of cases differed from that of other children in this tribe. This will now be given, with the proviso that any 'scheme' of this nature depends mostly on what food is in garden or store. The population is composed of peasants and they do not buy food. Great monotony may occur at certain seasons of the year when a glut of one foodstuff may prove the sole article of diet until the new harvest matures.

Kikuyu infants are always suckled; no other method of feeding is known. This is performed whenever the child cries. It is continued until the child is about one-and-a-half to two years of age, but ceases at once if the mother becomes pregnant. At the age of four, five or six months other articles of diet are added and pushed by anxious mothers into refractory babies. Gruel made from ground millet, with or without milk, is commonly given and soft chewed banana may be given by what could be accurately described as a mouth to mouth infection (it is expelled direct from the mouth of the mother to that of the infant). Later, at about seven or eight months potatoes are added, both the sweet African and the European varieties. Beans and whole maize grain are added during the second year. They are cooked in various ways and form with millet the staple articles of diet. Various leafy forms of native vegetables are taken cooked with the diet. None of the cereals are milled to remove the outer layers. Milk is not drunk except in small amounts by the children. Eggs are not taken. Fruit of any variety is exceptional. Practically all food is taken cooked, and cooked for long periods of time often with large addition of a coarse soda from the local source at Magadi. This is the cheapest form of salt. Meat is taken at rare intervals. Wheat and rice are luxuries for the few. This is the average diet of a Kikuyu child. Those who desire more information will find it fully discussed by Orr and Gilkes[23] who made a detailed investigation.

Maize is the staple cereal in all parts of the world where pellagra is common. The reason is not known. Orr and Gilkes criticized the Kikuyu dietary on the grounds that it did not contain enough animal protein, fat and calcium, and they believed that certain vitamin deficiencies might be present. Although vitamin B_2 was at first referred to as the heat stable factor in the B complex, more recent work has confirmed that it is rapidly reduced in an alkaline medium, Williams, Waterman and Gurin[38] and Chick

and Roscoe[4]. It is possible that the practice of cooking the food with Magadi soda may be one of the factors responsible for the appearance of pellagra.

Treatment

The treatment carried out in every case was the dietetic treatment of pellagra, as far as this was compatible with gastro-intestinal upset. Symptomatic treatment and that of the complications followed the usual lines. Pellagra appears to be a disease associated with, if not caused by, a deficiency of vitamin B_2 in a diet usually deficient in animal protein, of which staple cereal is maize. The slow adult form of the disease does not improve when small amounts of vitamin B_2, comparable with the amounts necessary to maintain health, are added. Larger amounts are necessary and even then the response is not dramatic and many patients die. The acute form of the disease in infants cannot be expected to respond to small changes, but only to specific changes, in the diet. Numerous observers have noted that the disease does not respond to a diet ' rich in vitamins ' and have concluded that the disease is not due to deficiency. When details of these diets are given they are found to consist largely of the vitamins A and D (cod-liver oil) and vitamin C (fruit juices).

Marmite was given in doses of a teaspoon a day for every year of age. Eggs and in severe cases liver were given. Milk one pint a day was drunk. Maize was eliminated from the dietary and replaced by wheat and rice. Other changes which were thought to be good, but are not regarded as essential now that the nature of the illness is thought to be known, were the addition of cod-liver oil and oranges. Iron in large doses for the anaemia and also calcium lactate were given as a routine mixture. Anorexia and indulgence by the mothers proved the greatest obstacles in the treatment. It proved necessary in these cases to separate completely mother and child and to forbid suckling. These small points unless duly appreciated will completely undermine any attempt to change the child's diet. Under this treatment only one case, admitted within a month of the onset, died, the remainder of these early cases were cured. Other observers who have not tried this form of treatment report that the disease is almost invariably fatal.

Discussion

Previous investigators in tropical Africa (Procter[25], Williams[35], Gillan[10], Stones[34], Carman[2] and Sequeira[27]) have concluded that the disease here described is not pellagra. They did this for two reasons; first, because the skin changes did not conform to the usual descriptions of pellagra, and secondly, because the unusual features of its incidence only in young children, its acute course, the absence of neurological signs, and the fatty stools could not be explained by pellagra. In addition, there must now be explained the presence of macrocytic anaemia, the fatty stools, and the atrophy of the thymus gland, which are the most obvious of the findings in this series but have not previously been recorded.

It is here contended that the skin changes are typical of pellagra—this point has been discussed already—and the gastro-intestinal symptoms, including fatty stools (Manson-Bahr[18]) are typical of pellagra, although in no former investigation of pellagra have fatty stools been so frequently observed. Manson-Bahr[18] also reports pallor of the skin and loss of hair in pellagrous children. The neurological findings are typical of pellagra and are here recorded for the first time. They are absent in the majority of cases because of the rapidly fatal nature of the illness. The pathological picture is consistent with acute pellagra, except that the atrophy of the thymus has yet to be explained, and there is still missing pathological proof of neurological change. Other anomalous features may now be considered.

The incidence in young children and its absence or profound rarity in the adult population cannot be explained because the facts on which it could be explained are not known with precision. Too little is known about native diet. The acute course of the disease may be explained by its incidence in young children, and an analogy can be drawn to ' pellagra typhus,' an acute febrile form of the disease which occurred during the great war among Turkish prisoners. The acute nature of the disease explains the absence of definite neurological signs, apart from hypotonia, in two-thirds of the cases.

The fatty stools cannot be easily explained. They are not commonly reported in pellagra, but all of these patients were being fed on milk and cod-liver oil, and the steatorrhoea is possibly only secondary to the enteritis. This point had not presented itself to the writer during the period of investigation but was made by Stannus. Further investigation is needed in this matter, and the absence of steatorrhoea in Williams's cases suggest that the cause may be dietetic.

Oedema is a striking feature of these cases and is not often found in pellagra. In descriptions of pellagra in children it is usually described as a mild oedema in a few of the cases. It cannot be explained by any of the usual causes, there being no evidence of cardiac or renal disease, of nephrosis, or ankylostomiasis. The anaemia does not appear sufficiently severe to explain it. There is no evidence of beri-beri, a rare disease where rice is not eaten, and there is no evidence of heart failure or neuritis.

It is however by no means certain that it is the absence of vitamin B_1 which is responsible for the production of oedema in beri-beri since Rosedale[26] found that rats and pigeons need a factor other than B_1 in the absence of which oedema occurred. This has been confirmed by Williams, Waterman and Gurin[38] and Peters[24]. Clinically the oedema of this condition may be regarded as comparable to the ' war oedema ' produced experimentally by Kohman[14] in rats. Both diseases are produced by a diet deficient in animal proteins. Bigland[1] has noted the fact that oedema is frequently a symptom of deficiency disease and Enright[6] found that the only deficiency disease associated with the ' war oedema ' cases was that of pellagra. Lastly, it is known that gastro-intestinal disease in infants is often complicated by oedema (Mavers[19]) and that diseases producing fatty stools, coeliac disease and sprue are often associated with this excess of fluids in the body tissues.

The anaemia when microcytic presents no difficulties and is only to be expected. Macrocytic anaemia may be explained along the lines of tropical macrocytic anaemia (Wills[10]) due to a deficiency of the vitamin B complex and cured by marmite. Later work has thrown doubt upon the hypothesis that the extrinsic factor of pernicious anaemia is vitamin B_{12}, but the original clinical finding of Wills still stands. Macrocytic anaemia is also found in pellagra (Stannus[33]). It is also well known that diseases associated with fatty stools are commonly associated with both microcytic and macrocytic anaemias.

The atrophy of the thymus gland may be correlated with the work of Williams and Crowell[37] who noted a similar change in polyneuritic chicken due to a deficiency of the vitamin B complex. The fatty and cellular degenerations of many organs (liver and intestinal mucosa) may be correlated with the findings of a variety of observers on vitamin B deficiency disease in animals, Funk and Douglas[9], McCarrison[21] and Findlay[8]. The increase in weight of the suprarenal glands and the presence of haemorrhages have been noted in the same diseased state by McCarrison[20] and Kellaway[13] and Korenchevsky[15].

It is therefore maintained that this syndrome in infants reveals with slight modifications the main clinical signs of pellagra, and that the unusual features can all be related to experimental conditions produced in animals subjected to a vitamin B deficiency in a diet also poor in animal protein. The syndrome is therefore an infantile variety of pellagra.

Differential diagnosis from pink disease

It may appear presumptuous to introduce to the notice of those interested in pellagra who have seen pink disease and have pronounced that the two diseases have no affinities that most observers of infantile pellagra in East Africa have noted the striking resemblance of mild cases of infantile pellagra to pink disease. It was mentioned originally by Gillan[10] and has been mentioned at numerous unreported clinical meetings at which the writer has been present. Manson-Bahr[18] mentions that the two diseases may be confused and in his opinion the distribution of the rash is similar in both diseases. Some have suggested that pink disease may be a deficiency disease. There is little agreement concerning its pathology, many regarding the changes in the central nervous system as those due to intercurrent infection.

Pink disease, lacking its essential colour changes in a negro skin, would be a difficult diagnosis in a native child and the writer believes that the only cases of pink disease in native children in Kenya have been reported by him, are listed as such in the official statistics, but all subsequently developed signs of ' infantile pellagra.'

A mild case of ' infantile pellagra ' presents a roughened desquamating skin, slight puffiness in all parts of the body, extreme petulance, photophobia, an irritable skin which is scratched, septic skin rashes, thinning of the hair and the nails, pronounced anorexia, cold clammy extremities, weakness of the limbs and marked hypotonia. Both diseases appear limited

to the same ages of from six months to five years. The diagnosis of ' infantile pellagra ' is made when any of the major signs, massive oedema, the rash, or gastro-intestinal signs occur. Before this in the opinion of the writer the two conditions cannot be distinguished.

In the uncertain state of knowledge concerning either pink disease or infantile pellagra further discussion is undesirable. Infantile pellagra was considered to have nothing distinctive in its pathology until Vint demonstrated the atrophy of the thymus, it was not considered due to a dietetic deficiency until marmite in massive doses and liver were shown to cure the disease in the early stages.

In conclusion it should be stated that the differences between pink disease and infantile pellagra are more obvious than the similarities. Briefly, infantile pellagra appears to be a grave deficiency, pink disease a minor deficiency. Pink disease occurs in European children, infantile pellagra among poorly fed, usually maize-eating African children living under deplorable conditions of health and hygiene. Deficiency diseases are known to be modified by other constituents of the diet; this may explain the different and yet allied symptomatology of pink disease and infantile pellagra.

Summary

1. Previous observations in Africa have revealed a syndrome in young native children characterized by irritability, oedema, gastro-intestinal signs and complex skin changes.

2. A detailed investigation of the clinical, bio-chemical and pathological changes was made in twenty-six cases with six post-mortem examinations in Nairobi, Kenya Colony.

3. In addition to the signs previously noticed by other observers, microcytic and macrocytic forms of anaemia were demonstrated, fatty stools were analyzed and neurological signs of hypotonia or of a hypertonia, increased tendon reflexes and an ' extensor ' response were demonstrated. The blood sugar curve was low. At post-mortem examination a remarkable atrophy of the thymus gland was demonstrated.

4. All the known clinical findings of pellagra were therefore present in this syndrome and the anomalous feature of oedema, anaemia and atrophy of the thymus can all be related to a deficiency of vitamin B_2 in a diet poor in animal protein, which deficiencies are more clearly related to pellagra than any other known disease.

5. Early cases were almost always cured by massive doses of marmite, liver, an increase of animal protein and the elimination of maize from the diet.

6. The points in which mild infantile pellagra may simulate pink disease are discussed. The attention of pathologists is invited to the post-

mortem appearances of infantile pellagra especially the atrophy of the thymus gland and of clinicians to the effect of massive doses of marmite and liver lest either of these might prove relevant in pink disease.

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VITAMIN B_1 DEFICIENCY IN INFANCY

A CRITICAL REVIEW

BY

M. R. PRICE, M.B., D.C.H.

Whether vitamin B_1 is deficient or not in normal diets in this country is open to doubt. It is probable that at times when added amounts of B_1 are required, as for instance in childhood, adolescence and during pregnancy and lactation, many persons would benefit from additional B_1 and some ill health might be preventable by addition of this vitamin to the diet. It has been calculated by Cowgill that B_1 requirements are proportional to metabolism. The amounts required daily by an adult weighing ten stone have been variously stated. They are thought to be in the region of four hundred and fifty to one thousand five hundred international units rather than two hundred as was previously suggested. The pregnant and lactating woman seem to require something in the region of one thousand international units daily for optimal well-being. The amount required by an infant has not been ascertained, but a child appears to require relatively more than an adult for each pound of body weight; four hundred international units has been suggested for a child of four and six hundred and eighty for a child of eleven years. Increase of weight would seem to need increase of vitamin B_1. A diet of high caloric value requires this vitamin for its utilization. Vogt-Müller[1] states that the more carbohydrates a diet contains the greater the requirements of B_1 and this agrees with experimental work on animals.

Recent literature

A study of the recent American literature on vitamin B_1 brings out clearly how large a measure of agreement there is among various investigators concerning the prevalence of minor degrees of B_1 deficiency especially in children. This view is now supported in England by Peters[2] and Pritchard[3]. Addition of substances rich in B_1 is advocated in the section on normal diets in a recent text book of paediatrics[4]. In the Medical Research Council's Report on Vitamins it is suggested that as a safeguard against possible deficiency a rich source of B_1 should be given to all children. With regard to infants there have been constant references in the American literature[5] since 1929 to the fact that infants receive less than the optimal amount of vitamin B_1. Sure, Macy, Lemester and Bloxom[6, 7] have carried out experiments on infants and young children and show that those receiving a supplement of vitamin B_1 to their normal good quality diet thrive

better than the control subjects. Sure goes so far as to say that ' Perhaps millions of lives may be saved by employing vitamin B_1 as routine to the extent that orange juice and cod-liver oil are used '[8]. Bray found marked benefit from giving added B_1 to infants in the Pacific Isles.

Amounts required

Adequate amounts of vitamins are recognized as being essential to health and the B group is thought to be the one most likely to be supplied in deficient amount[9]. Vitamins A, D, and C are prescribed for most bottle-fed babies but of B_1 the infant receives only the small amount present in the milk formula after the cow's milk, which is not a rich source of this vitamin when raw, has been dried or evaporated: and a further fraction from the orange juice given for its vitamin C content. The optimal amount of vitamin B_1 has not been ascertained for the infant. A child of four is thought to require four hundred international units daily. Since the metabolism of the infant is greater it is possible that it requires relatively more of this vitamin. An infant receiving only a milk mixture is likely to require about two hundred international units a day for optimal well-being. Increased carbohydrate in the diet necessitates a greater intake of vitamin B_1. The diet of an infant less than six months old contains a greater proportion of carbohydrate than does that of a child aged one year. This figure of two hundred international units is twice that suggested by Pritchard for children under one year. He does not state, however, by what means he arrived at his estimate of one hundred international units daily[10].

The amounts required at different ages and under various conditions fluctuate widely. Thus it has been estimated that pregnant and lactating animals (rats) need five times as much vitamin B_1 as they require when not in this condition. This is found also to apply to the human[11]; pregnant and nursing women have a greatly increased need of B_1.

Symptoms of deficiency

It has recently been suggested that B_1 deficiency may be a major factor in the causation of the symptoms of pregnancy toxaemia. The amount calculated as adequate for both mother and child when the latter is breast fed is in the neighbourhood of one thousand five hundred units[12]. As extremely few nursing mothers receive even half this amount, it is not surprising to find that breast milk contains considerably less vitamin B_1 than does cow's milk and the assumption that breast-fed infants are at least as short of this element as bottle-fed babies has therefore much to support it.

Although symptoms of gross deficiency are not seen in this country, a large number of symptoms have been attributed to minor degrees of vitamin B_1 shortage. This varied symptomatology leads to widely differing clinical pictures from the well-defined syndrome such as pink disease and

the indefinite but frequently met with condition called debility or ' failure to gain weight.' The description given by Hoobler, of Detroit, of a case of infantile beri-beri has suggestive points of similarity with the infant who is just ' not getting on ' as will be seen from the following tables:—

Infantile beri-beri.	The infant failing to thrive.
Vomiting and constipation.	Vomiting and constipation.
Fretfulness.	Fretfulness.
Restlessness.	Restlessness.
Waxy look.	Pale.
Whining cry.	Cries pitifully.
Colic, ' blue turns.'	Colic.
Convulsions.	

Symptoms of minor degrees of deficiency in animals vary considerably according to the kind used. Thus in rats anorexia, a staring coat, failure to gain weight and finally death from inanition are described, even though at post mortem the stomach may be full of curds. In monkeys diarrhoea is a frequent early symptom and dehydration may become marked[13]. In this respect some work done on dogs is of interest, as it is found that in animals suffering from mild avitaminosis (B_1) the symptoms are increased by giving water freely without food[14]. If it is true that many infants at the present time are receiving sub-optimal amounts, these results may have some bearing on the symptoms and treatment of gastro-enteritis in infancy. Rats reared on a diet deficient in B_1 are said to be inferior in ' maze learning ' to those fed on a diet containing in addition adequate amounts of this vitamin[15].

The actions of the B_1 fraction of the vitamin B complex have not been fully determined but the following have been attributed to this substance by several independent workers.

1. Muscle tonus especially of the intestinal tract is increased; vitamin B_1 is thought to correct anorexia and constipation through this action, as ' hunger contractions ' of the stomach are absent in animals on a B_1 deficient diet[16].

2. Carbohydrate metabolism is dependent on the presence of B_1 for its completion of the oxidation process. The vitamin is thought to act as a catalyst. In deficiency states the lactic acid produced by muscular activity accumulates there and is only very slowly oxidized and removed, thus leading to fatigue, atony and possibly to the accumulation of toxic end-products of metabolism[17]. The bradycardia of rats on a B_1 deficient diet used as a method of standardization is thought to be due to this accumulation of lactic acid in the heart muscle.

3. Vitamin B_1 has some essential part in the well-being of the lymphoid tissues. In animals fed on diets deficient in B_1 the lymphoid tissue throughout the body atrophies leading (a) in the bowel to impaired assimilation of food, (b) to generalized lymphopenia[18].

From a consideration of the above actions it is reasonable to suppose that the result of adding vitamin B_1 to the diet of infants and children would be an increase in appetite, and in assimilation and utilization of food, thus producing an increase in weight and height. Many large scale experiments have been carried out in America and show quite conclusively that the

expected result is indeed a fact[19]. Infants and children up to two years of age, gain seventy per cent. more if supplied with additional vitamin B_1. Since in each case the diet appeared to be of good quantity and quality before the addition of vitamin B_1 it is reasonable to suppose that in this country also many children and infants are receiving less than optimal amounts of this substance.

It seems desirable to put this suggestion to the test by adding vitamin B_1 to the food of a group of nurslings and comparing their progress with a control group. These observations are now being made.

Summary

From a survey of the literature it would appear that:—

1. The amount of vitamin B_1 required by a nursling is about two hundred units a day.

2. Many nursing mothers do not have sufficient vitamin B_1 in their food to pass on an adequate supply to their babies.

3. By analogy from animal experiments some common infantile ailments may arise from deficiency of vitamin B_1.

4. There is sufficient evidence to make feeding experiments on young infants desirable.

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VARIATIONS IN THE FIRST HEART SOUND AND THE AURICULO-VENTRICULAR CONDUCTION TIME IN CHILDREN WITH RHEUMATIC FEVER

BY

J. D. KEITH, M.D.*

(The Birmingham Children's Hospital.)

It is well recognized that a soft first heart sound is frequently found in rheumatic heart disease in children. When this has been marked it has been presumed that a severe degree of carditis existed. It is the purpose of this paper to point out certain relationships regarding the soft first heart sound and the accentuated first sound in rheumatic fever and discuss the reasons for their occurrence.

Coombes[3] in his book on 'Rheumatic Heart Disease' says 'In very acute carditis the first sound at the apex may become softened and almost inaudible; this used to be accepted as evidence of pericardial effusion until it was shown that this complication was extremely rare. At the same time it became apparent that enfeeblement of the myocardium was at the bottom of the signs wrongly ascribed to pericardial effusion. It occurs only in the severest types of carditis and is to be interpreted as a direct sign of grave failure of ventricular contractivity.' Cabot[2] in 'Physical Diagnosis' refers to weakening of the first sound at the apex as occurring in the course of long-continued fevers in which there is degeneration of the heart muscle. He concludes 'All in all however these changes in the first sound are of very little diagnostic use.'

Present investigation

It was noticed that cases of acute rheumatic fever that had softening of the first heart sound at the apex were frequently not of a severe type, and for that reason the question has been investigated.

A case that illustrates this is that of O. O., aged 10 years, who was admitted to the Birmingham Children's Hospital suffering from chorea. There was no evidence of heart disease on admission. During her stay in hospital she developed a transient mild carditis of a degree that presented only the faintest signs. The intensity of her first heart sound became fainter

* Working under an Atholl-Moynihan Scholarship, University of Birmingham, in the Rheumatic Research Department.

as the P-R interval lengthened and improved as it shortened. These findings are recorded in the following table:—

Date.	Sedimentation rate.	Heart rate.	P-R interval seconds.	First sound.	Murmurs.
Admission	—	100	0·15	Full. Well heard.	None
10 days	—	94	0·18	Diminished.	None
22 days	5 mm.	92	0.20	Almost inaudible.	Very faint systolic.
1½ months	6 mm.	85	0·18	Diminished.	None
2 months	—	90	0·16	Blunt. Distinctly heard.	None
2½ months	—	90	0·15	Full. Well heard.	None

Blood leucocyte count at 5 weeks—10,800 per c.mm.

The first heart sound has been studied in over two hundred children with chorea, chorea with rheumatic carditis and in cases of uncomplicated rheumatic carditis. In the same series of cases repeated electrocardiographs have been studied and ventricular conduction time has been noted. A group of sixty-two patients of rheumatic heart disease with P-R intervals over 0·18 seconds were investigated in detail. These were divided into two groups, those in their first attack of carditis and those that had previously had attacks.

Group 1. First attack of carditis.—There were thirty-seven cases of rheumatic fever with a first attack of carditis in which the conduction time exceeded 0·18 seconds.

Average age 8·4 years. Range 3 to 12 years.
Average sedimentation rate 28 mm. per hour. Range 3-60 mm. per hour.
32 mild cases.
3 moderately severe cases.
2 severe cases.

Four of these children showed mitral diastolic murmurs, in two, such murmurs were temporary and disappeared within two months. The first sound was markedly diminished in intensity, and in many cases was inaudible, while twenty-one had an apparent accentuation of the second sound in the mitral area.

In this first group most of the patients were only mildly ill and the pulse rate fell below 100 to a level practically normal within a few days of admission. The temperature was as a rule elevated only on the day of admission or on some days previously at the onset of their rheumatic attack. The soft first sound usually persisted for one to two months and then became more normal in intensity. The second sound at the apex was in many cases well heard and often sounded accentuated because of the diminution of the first. In this group the heart was rarely enlarged beyond

a minor degree. All had systolic murmurs at the apex and a few of these disappeared during the hospital stay. In two cases the conduction time continued to be 0·2 seconds after the systolic murmur had disappeared and the only clinical evidence of heart disease then was a soft heart sound.

It was found then that many cases of acute rheumatic fever have a conduction time of 0·2 seconds without having the most severe form of carditis. Thirty-two cases out of thirty-seven had a relatively mild lesion, and the softened first sound appeared to be associated only with the lengthened conduction time, rather than myocardial weakness.

Dock[1] has summarized the experimental evidence on the mode of production of the first sound and conducted some interesting experiments along these lines. Using anaesthetized dogs and recording heart sounds by a modification of the method of Wiggers and Dean he recorded heart sounds (1) with the venous return clamped and (2) with a ligature round the auriculo-ventricular ring. In both instances the heart continued to beat for some time but the heart sounds were practically eliminated. In the first instance there was an average of 95 per cent. reduction in the amplitude of the sound of vibration produced at the beginning of systole, while the ligature around the auriculo-ventricular ring reduced the amplitude by 93 per cent. He says 'Not only was the amplitude diminished but the recorded vibrations were so different in form from those recorded from the hearts before the circulatory condition was altered as to leave no doubt that in clamped off or ligatured hearts the recorded vibrations were inaudible mechanical effects of ventricular movement.' He concludes that the first sound is due to putting under high tension suddenly the previously slack fibres of the auriculo-ventricular valves.

Ruanet in 1832 first expressed the theory that the sudden tension of the auricular-ventricular valves is an important factor in the production of the first sound. In 1851 Halford[5] recorded experiments on a dog in which clamping off the venous supply caused the first sound to disappear.

From these experiments it is seen that vigorous systole produces no appreciable sound. Furthermore, that the theory that the first sound is due to the tensing of the heart wall around its incompressible contents is disproved by the fact that little or no sound was produced when the auricular-ventricular ring was ligatured in Dock's experiments. Dock[4] uses the old example of a handkerchief or string to explain the mode of production of the first sound. When the border of a handkerchief is suddenly drawn taut it produces a sound like that of the first heart sound, and he points out that if a piece of carpet or strips of meat as thick as the left ventricle are used such a sound cannot be artificially produced. In the question of intensity of the first sound the valvular theory suggests that if the auricular-ventricular valves are lax and suddenly drawn taut a sound is produced normally. If, however, they are already closed and part of the tension taken up at the beginning of ventricular systole no sound occurs. Using the analogy of the handkerchief if the slack is taken out quickly a noise is made similar to the first sound. If, however, the slack is taken out gradually at first and then sudden tension produced even with great force no sound results. Applying this to the study of the first sound and the

auricular ventricular conduction time, in the children with a P-R interval of 0·2 seconds the mitral valve would be permitted to close and the tension partly taken up before ventricular systole occurs, and the first sound is soft. Kerkhof[7] has shown that when patients with mitral stenosis go into auricular fibrillation the cardiac minute volume diminishes about 22 per cent. and concludes that auricular systole adds approximately this much to the cardiac output. In a normal heart the ventricle is partially filled in diastole before auricular systole takes place. If auricular systole then adds 22 per cent. to the ventricular volume the tension is considerably raised and would result in closure of the auricular ventricular valves and put them under a moderate degree of tension. If ventricular systole occurred after this process was complete the auricular-ventricular valves would contribute little to the first heart sound. This appears to be actually what takes place in these children with lengthened P-R intervals and a poor first heart sound results.

In the thirty-seven cases of acute rheumatic fever in the first attack in which the conduction was over 0·18 seconds, all had marked diminution in intensity of the first sound; in many cases the first sound was practically inaudible. The clinical significance is indicated by the fact that in 100 cases of rheumatic heart disease investigated at this hospital it was found that 26 per cent. had P-R intervals of 0·2 seconds or over at some time over a period of two years: 52 per cent. had P-R intervals of 0·18 seconds or over, and it has been found that these conduction changes can be determined with a moderate degree of accuracy with the stethescope. Heart sounds were studied in many cases that had shorter P-R intervals and the following scheme is recorded to indicate the relationship of the conduction time to the first heart sound. This scheme cannot be applied with mathematical accuracy, but holds true generally.

Λ Λ	Λ̄ Λ	∩ Λ	⌒ Λ	⌣ Λ
0·12 Sharp first sound.	0·14 Moderately sharp first sound.	0·16 Full or blunt first sound.	0·18 Diminished intensity of first sound.	0·20 Very faint or inaudible first sound.
First sound greater in intensity than second.		First and second equal.	Second sound greater in intensity than first.	

These variations in the first sound related to the P-R interval are not as useful when the P-R is 0·16 or less. When the conduction time is more than 0·16 seconds, diminution in the intensity of the first sound in cases of rheumatic heart disease in their first attack is almost invariably found provided certain factors are eliminated. It must be emphasized that these factors must be taken into consideration or eliminated before the intensity of the first sound can be evaluated. Thickness of the chest wall, the presence of pericardial or pleural effusion or emphysematous lung tissue,

heart rate and degree of damage of the myocardium are the chief factors in altering the intensity of the first sound other than the conduction time. In children the chest wall is thin and change in the heart sounds can be much more readily discerned than in the adult. In rheumatic fever pericardial effusion is rare. The myocardium is as a rule not so severely damaged in the first attack of rheumatic fever as to produce a resulting myocardial weakness, and does not play a very large part in changing heart sounds at this stage. Increased heart rate will augment the intensity of the first sound and this must be taken into consideration. A heart rate of less than 100 beats per minute will not usually interfere with interpretation of the first sound in relation to the conduction time. In children with mild rheumatic heart disease by far the most important factor in producing softening of the first sound is alteration in the conduction time.

Group 2. One or more attacks of carditis.—Twenty-five cases of rheumatic fever which had previously had one or more attacks of heart disease and which had conduction times over 0·18 seconds.

Average age 10 years. Range 6 to 13 years.
Average sedimentation rate 38 mm. per hour. Range 15-60 mm. per hour.
6 mild cases.
7 moderately severe cases.
12 severe cases.
14 cases had mitral diastolic murmurs.
4 cases had accentuation of the first sound, in the rest the first sound was practically inaudible or ' replaced.'

This second group is comprised of more severe cases as would be expected in rheumatic patients who had had more than one attack of carditis. In the majority the hearts were appreciably enlarged and the murmurs indicated damage of sometime standing to the valves. Twelve were severe cases (judged by demonstrable lesions and recent acute infection together), seven moderately severe and six mild cases. Fourteen had mitral diastolic murmurs which appeared to be permanent.

The diagnosis of mitral stenosis is made in a case of rheumatic heart disease on the sum of several pieces of evidence. The most important are accentuated first heart sound, mitral diastolic murmur and forceful apex beat accompanied by thrill. The last is not essential for the diagnosis and most emphasis has been placed on the presence of a mid-diastolic murmur, or an auriculo-systolic murmur. Certain of these diastolic murmurs are recognized by their sound and intensity as characteristic of obstruction at a grossly narrowed valve lumen in the heart, and leave no doubt as to the diagnosis. However, it has been frequently noted by many observers that a mitral diastolic murmur may exist in cases of rheumatic heart disease in which no stenosis of the mitral valve is apparent at post-mortem examination. Further, diastolic murmurs occur sometimes in patients with heart disease of other than rheumatic origin.

The question of mid-diastolic murmurs in rheumatic heart disease has been thoroughly dealt with by Bland, White and Jones[1]. From a clinical and post-mortem study of a hundred patients under twenty-one years of age it was shown that in many cases diagnosed clinically as mitral stenosis the diagnosis was not borne out at autopsy. They discuss the significance of a mitral diastolic murmur and pointed out that it could not be used as an infallible sign of mitral stenosis. It was not uncommonly found in the early stages of their cases of rheumatic heart disease (the minimum time for mitral stenosis to develop they found was two years) and often disappeared during convalescence. They believed myocardial weakness and dilatation of the ventricle to be responsible in their cases for its production, for this is generally accepted now as the most probable explanation of this transient diastolic murmur. In the hundred cases studied mitral stenosis was considered to be present clinically on the basis of the mid-diastolic murmur best heard at the apex in sixty-eight cases. It is interesting that they record that of these only twenty-one had anatomical stenosis at post-mortem examination.

Since so many of the signs of mitral stenosis are fallible the value of the accentuation of the first heart sound of the fourteen cases in the present group with mitral diastolic murmurs must be discussed. Only four had an accentuated first sound, several of the others had accentuation of the first sound on admission but when the heart approached a more normal rate the first sound disappeared or became very faint. These probably had no anatomical narrowing of the mitral orifice but undoubtedly had valvular damage. When these hearts are beating rapidly the first sound has exactly the same slapping quality of the first sound in mitral stenosis. However, because of the gross enlargement of these hearts the mitral opening is not infrequently larger than normal. The four cases with an accentuated first sound at all rates of the heart may be diagnosed as having mitral stenosis.

The mechanism of this accentuation in mitral stenosis is closely related to the experiments, mentioned above, by Dock. In mitral stenosis the peak of intra-auricular pressure may occur later to be sustained longer than in normal hearts. When the passage of blood from the auricle to ventricle is impeded and the pressure from the auricle is forcing blood through the narrowed opening, the mitral valve is extended into the ventricle as far as its limited capacity permits and when ventricular systole occurs it is suddenly slapped in the opposite direction. This results in the accentuated first sound, and when mitral stenosis is present one nearly always hears this accentuated first sound. If the P-R interval was sufficiently long the ventricle could be filled and the slack taken out of the valves before the beginning of ventricular systole. However, Wolferth and Margolies[7] found in cases of mitral stenosis accentuation was still present when the P-R was 0·23 seconds. When complete block supervenes one gets a varying intensity of the first sound depending on the relation of auricular and ventricular pressure at the time of ventricular systole.

In children mitral narrowing is more likely to occur if the valvular damage far outstrips the myocardial damage. In this case the evidence of

mitral narrowing might be a well heard first sound with a moderately prolonged P-R interval, when otherwise a soft or absent first sound would be expected, but since the usual process in severe rheumatic fever in children is for the myocardial damage far to outstrip the valvular and therefore there is a widening of the auricular ventricular opening and not stenosis.

In the twenty-one patients without diastolic murmurs but who had had more than one attack of rheumatic fever the first sound was not heard and these fall into the same category as group 1. These are described as having the first sound replaced by a murmur, but it was found in a number of these cases that the P-R interval at a later date became shortened again. When this occurred the first sound could be readily heard although the murmur remained unchanged. Occasionally these enlarged hearts have the first sound ' replaced ' when the P-R interval is only 0·16 seconds. Such cases are difficult to explain adequately, but it is probably due to the degree of dilatation present.

In interpreting these sounds and murmurs it is worth while noting the findings in the second group reported by Bland, White and Jones[1]. These were patients who had definite deformity of the mitral valve without anatomical stenosis. They found that the degree of mechanical handicap imposed on the heart appeared to be the same as in the group with mitral stenosis, so from the point of view of prognosis accurate diagnosis of the anatomical narrowing of mitral stenosis is not of prime importance as long as the nature of the lesion is understood.

Summary

The relationship of the intensity of the first heart sound to the P-R interval is discussed and the experimental results of Dock are applied clinically to cases of children with rheumatic heart disease of various degrees of severity. It is found that the P-R interval can be predicted with a fair degree of accuracy by the intensity of the first heart sound. This is of most value in the milder cases. The clinical significance of this is emphasized by the fact that in a hundred cases of rheumatic heart disease investigated at this hospital, it was found 26 per cent. had P-R intervals of 0·2 seconds or over at some time during a period of two years. Fifty-two per cent. had P-R of 0·18 seconds or more over the same period. In the past too much emphasis has been placed on heart murmurs in rheumatic carditis and evidence has been presented in this communication of the definite importance of heart sounds. The accentuated first sound of mitral stenosis is discussed and it is suggested that the presence of this sign in rheumatic children (provided the heart rate is not notably raised) is more valuable in the diagnosis of mitral stenosis than the mid-diastolic murmur.

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DYSENTERY IN INFANCY

BY

I. A. SABRI, M.R.C.P., D.T.M. & H., Assistant Physician; M. A. ABBOUD, M.R.C.P., Resident; and M. ALI, M.B., B.Ch., D.T.M. & H., Bacteriologist.

(From the Paediatric Department, Faculty of Medicine, Cairo.)

Dysentery is a common disease in Egypt. It affects children of all ages, but is most frequently encountered during the first two years of life. Thus, of 14,304 cases of dysentery examined at Fouad I Children's Hospital, during the last three years, 60 per cent. were in the first two years of life, 30 per cent. in the third to the sixth year and 10 per cent. in older children. The disease occurs sporadically during the whole year, but shows a marked increase during the hot summer months. Of the above mentioned 14,304 cases, 58 per cent. occurred in the four hot summer months of the year (May–August). Both breast- and artificially-fed infants suffer from the disease. The latter, however, are more commonly affected. Thus, of 3,000 infants below the age of one year who suffered from dysentery, the incidence of the disease was six times as great in artificially-fed infants as in the breast-fed. As in the case of other infections dysentery presents in infancy many of the features peculiar to this age period. With the aim of recording some of these features, the results of investigations carried out on a series of 100 cases of acute dysentery in infants and children under two years of age are presented.

Diagnosis

For the purpose of diagnosis a thorough stool and sigmoidoscopic examination was carried out in every case of the series. The latter method of examination was repeated regularly during the whole course of the disease in order to follow the progress of the cases closely.

(A) **Stool examination.**—The naked eye differences often described[1, 2] between amoebic and bacillary dysentery stools could not be clearly made out, and all attempts at such differentiation were unsuccessful. The cytological picture of the stools on the other hand, was of great help in the diagnosis. In many of the cases in which neither dysentery bacilli nor entamoebae were detected, the cellular picture of the stools was of value in suggesting the type of infection present. The advantages of making cultures as early as possible in the course of the disease are illustrated in the cases investigated. Seventy per cent. positive results were obtained from the cultures made in the first five days, fifty per cent. in the second

five and only twenty-six per cent. in the third five days of the disease. The corresponding figures obtained by Martin and Williams[3] were 68 per cent., 17·4 per cent. and 6·3 per cent. respectively.

In the following table are recorded the results of stool examination of the series of cases investigated:—

B. dys. Flexner group	24
B. dys. Shiga	4
B. dys. Sonne	3
B. dys. Schmits	1
B. Morgan No. 1	10
B. paratyphoid A	1
B. faecalis alk.	6
Strept. faecalis	7
B. paracolon	4
Ent. histolytica	5
Mixed infections (Ent. hist. + B. dys.)	5
Intestinal flagellates	6
Not identified	24
Total ...	100

It is evident, from the above table that both amoebic and bacillary dysentery are met with in infancy. The bacillary form, however, is by far the most common. In addition to the accepted causal organisms of dysentery, B. Morgan No. 1 and B. paratyphoid are considered by many workers[4, 5, 6] as possible causes of the disease in early childhood. The rôle played by Strept. faecalis, B. faecalis alk. and B. paracolon in the aetiology of dysentery is not quite definite. These organisms are recognized by some investigators[5, 7] as causes of diarrhoea and dysentery. In the six cases in which intestinal flagellates alone were found on stool examination, the presence of lesions in the bowel characteristic of amoebic (two cases) and bacillary (four cases) dysentery could be demonstrated. Intestinal flagellates, however, are considered by many writers[4, 8, 9, 10] to be able to produce diarrhoeic and dysenteric symptoms in children.

(B) Sigmoidoscopic examination. – The experience obtained with the sigmoidoscope in the last few years in the diagnosis of affections of the large bowel has proved the great value of this instrument. On the whole, the sigmoidoscope affords a better and more rapid means of accurate diagnosis of the type of dysentery present than any other available means. Thus, whilst an accurate diagnosis of the type of dysentery could be arrived at by the sigmoidscope in 100 per cent. of the cases, a positive result was obtained by stool examination in only 74 per cent. Friedemann[11] and Biggam and Arafa[12] arrived at similar results in adults. The use of the sigmoidoscope in children is practically devoid of danger. The youngest infant of the series on which sigmoidoscopy was performed was two months old. Elaborate preparation of the patient, although a necessary step in the adult, is often not required in the child. The child is given in the early morning a simple water enema. Two or three hours later,

sigmoidoscopic examination is carried out. The child is laid on his right side with the knees drawn up and the buttocks close to the edge of the table. This position is convenient to the patient and enables the nurse to have a good hold of the child. Sedative drugs were never needed.

Appearances. Before an attempt is made to describe the pathological appearances of the bowel in infants as seen through the sigmoidoscope, the normal picture must be known. For this purpose, thirty healthy infants below the age of two years, who had not suffered from any intestinal disturbance during the last three months, were investigated. The stools were examined and sigmoidoscopy was performed in the usual way. The mucous membrane of the bowel appears of a pink colour with a shiny, smooth surface and visible subepithelial venules. The colour of the bowel wall was compared with the various gradations of a haemoglobin scale (Tallqvist) and was found to correspond to 40–50 per cent. Hb. In bacillary dysentery the mucous membrane of the rectum and colon appears congested. The surface has lost its glossiness and bleeds easily on the slightest touch with the instrument. The subepithelial venules are no longer visible. In severe cases, whitish, necrotic patches are seen. They are superficial and after separation leave superficial erosions. The congestion is always more marked in the lower than in the upper parts of the colon. In mild cases, it extends only a short distance up the bowel and fades gradually into normal mucosa; but in severe cases, the congestion extends beyond the reach of the sigmoidoscope (8 inches). In cases of moderate severity, the colour of the inflamed mucosa corresponds to 70–80 per cent. Hb., whilst in severe cases it may reach 100 per cent. In amoebic dysentery on the other hand, the sigmoidoscopic appearances are quite different. The mucous membrane retains its normal pink colour, the surface remains shiny and the subepithelial venules are visible. Scattered here and there over the healthy mucosa are seen yellowish spots and small rounded or oval ulcers ($\frac{1}{8}$–$\frac{1}{4}$ inch) surrounded by congested areolae. The base of the ulcer is often covered with a yellowish-white exudate. The most common site for these ulcers is the lower part of the rectum and especially just inside the internal sphincter. On scraping these ulcers, living amoebae, often in large numbers, are obtained. Mixed forms of bacillary and amoebic dysentery are not uncommon. The sigmoidoscopic appearances are a combination of the above two types.

Five cases of mixed infection were met with; they were as follows:—

Ent. hist. + B. dys. Sonne	...	...	1 case.
,, ,, + ,, ,, ,, + Morgan 1	...		1 ,,
,, ,, + ,, ,, Flexner	...	...	3 cases.

The information obtained from the sigmoidoscopic examination, may be summarized as follows:—

(1) An accurate diagnosis of the form of dysentery could be arrived at in all cases.

(2) The severity of the local conditions has no relation to the causal organism. The same organism may produce the most severe or the most

mild inflammation. Organisms to which mild forms of dysentery are usually ascribed could produce the worst type of inflammation and vice versa.

(3) There is no intimate relationship between the severity of the local condition of the bowel and the general symptoms of the disease. In some cases with symptoms of marked general disturbance, the local condition of the bowel was by no means severe.

(4) Infection with more than one organism does not necessarily give rise to more severe affection of the bowel than others produced by one single organism.

(5) The return to normal of the bowel condition as seen by the sigmoidoscope was always later than that of the stools. The average interval was five days. In some cases, however, the interval was as long as nineteen days. O'Connor[13] recorded observations on cases in which ulceration of the colon was still present after complete clinical cure. This is a point of some clinical importance. It shows that clinical cure of dystentery precedes the onset of actual cure of the bowel.

(6) Relapses always occurred before the onset of complete cure of the bowel as judged by the sigmoidoscope. Their occurrence was accompanied by aggravation of the local condition of the bowel.

Clinical features

Clinically, two main forms of the disease could be distinguished:—

(A) **A simple form** in which the local intestinal symptoms were the prominent feature. This constituted the majority of the cases (85 per cent.). Apart from the characteristic stool picture, abdominal pain and occasional vomiting, the general condition of the child was not much affected. To this form belong cases of amoebic infection, and the majority of bacillary cases of mild or moderate severity.

(B) **A toxic form** in which symptoms of intoxication predominated. It accounts for 15 per cent. of the cases. In these the general symptoms of dehydration, disturbed consciousness and toxic respiration were prominent. They were all bacillary cases, and the causal organisms were:—

B. dys. Shiga	3 cases (out of 4 in the whole series)	(1 died)
B. dys. Flexner	4 cases	(1 died)
B. dys. Sonne	1 case	(1 died)
B. Morgan	2 cases	(1 died)
Not identified	5 cases	

It is evident from the above that the majority (75 per cent.) of Shiga infections are of the severe form of dysentery. The other habitually less toxic organisms, however, could also produce severe forms of dysentery and, in fact, they account for the majority of toxic cases (80 per cent.) in the present series.

This may also explain the failures frequently obtained by the treatment of dysentery in infancy by the administration of antidysenteric serum. Serum, as is well known, is most potent against infections with the Shiga bacillus. Its effects in dysenteries due to other organisms are much less striking. Since the majority (80 per cent.) of the severely toxic cases of

infantile dysentery are produced by organisms other than B. dys. Shiga, little is to be expected from the use of serum in most cases.

Complications.—The complications met with in the above cases were as follows:—Bronchopneumonia, 2 cases; oedema, 3 cases; pyuria, 19 cases (pus cells exceeding 50 per c.mm. of uncentrifugalized urine); and prolapse of rectum, 15 cases.

Duration.—The duration of the diseases in bacillary cases was not intimately related to the causal organism. Cases due to Flexner infection, for example, lasted a variable time between eight and twenty-two days. Those due to other organisms also showed similar variations. The duration of the disease in the cases of bacillary dysentery that were completely cured (sigmoidoscopically) before discharge was as follows:—7–10 days in 7 cases; 11–20 days in 50 cases; and 21–28 days in 19 cases.

Relapses.—Recurrence of symptoms with the reappearance of dysenteric stools occurred in nine cases. They all occurred after apparent clinical cure before the onset of actual cure of the bowel. The symptoms lasted for a few days and were accompanied by some aggravation of the bowel condition. No dietetic faults were responsible for these relapses. This agrees with the experience of Albert and Quiason[14] and Meyer and Nassau[15].

Dietetic therapy

With the exception of amoebic cases, which received in addition specific drugs, the treatment adopted was purely dietetic. Drugs of known action on the bowel such as cathartics and astringents, were not used. Anti-dysenteric serum was not administered in any case. The repeated failure of serum therapy in infantile dysentery experienced in the Fouad I Children's Hospital, Cairo, and reported by many other workers[12, 13, 14] encouraged this step. The diet used in each case was studied from the point of view of its effect on the general condition of the child, as well as on the local condition of the bowel.

The lines of treatment may be summarized thus:—

(a) A preliminary stage of complete starvation of six to twelve hours, during which boiled water or weak infusions of tea or caraway sweetened with saccharin is given.

(b) An intermediate stage of milk-free diet during which concentrated rice gruel 10 per cent. (after Bessau[16, 17]), sweetened with 5 per cent. dextrimaltose, is given at three or four hourly intervals. Abundant amounts of fluids are offered between the feeds. The duration of this stage varies between one and three days according to the severity of the symptoms and the state of nutrition of the child.

(c) The third stage, during which milk or some other food is gradually introduced after the step-ladder scheme of Finkelstein.

(d) A final stage of return to normal diet is not attempted until complete cure, as judged by the sigmoidoscope, is established.

Amoebic cases, in addition to dietetic treatment, received injections of emetine hydrochloride ($\frac{1}{6}$ grain daily for six days) combined with enemata of a 2 per cent. solution of yatrin 105.

The diets used in feeding the above cases were:—

1. HUMAN MILK. Breast-fed infants were continued on the breast. After a short period of starvation, the child was given the breast for gradually increasing periods. Toxic cases were given expressed human milk in smaller quantities.

2. BUTTERMILK. This was given to artificially-fed infants below the age of six months. Powdered buttermilk (Beurlac, Cow & Gate) was used in one in ten dilution. Rice gruel 2 per cent. was used as the diluent and 5 per cent. dextrimaltose was added.

3. PROTEIN MILK. This was given to artificially-fed infants above the age of six months. Powdered protein milk (Prolac, Cow & Gate) was prepared in the same way as buttermilk and in a dilution of one in twelve.

4. APPLE DIET (modified from Heisler and Moro). This was given to children above one year of age. In the first two days scraped raw apple or Aploma powder 8 per cent. suspension, was given in five meals. In the subsequent days, sweet white cheese, dry toasted bread (Zwieback), mashed bananas, boiled lean minced meat, mashed potatoes, boiled rice, vegetable purée were gradually introduced.

5. CARBOHYDRATE DIET. This was given to another group of children similar to those given apple diet. After a day or two on rice gruel, 10 per cent. sweetened with 5 per cent. saccharose, a diet rich in carbohydrates was given consisting of arrow-root made rather thick, boiled rice, toasted bread and mashed potatoes. Purée vegetables and milk were given later.

In the following table are shown the results of the treated cases:—

Diet.	Cases.	Weight. Gain.	Weight. Constant.	Weight. Loss.	Stools. Return to normal.	Sigmoidoscope. Return to normal.
1. Human milk	20	1	12	7	after 8 days	after 11.6 days
2. Protein milk	20	10	5	5	after 6.3 days	after 13 days
3. Butter milk	16	6	6	4	after 6.6 days	after 12.3 days
4. Apple diet	10	7	3	0	after 6 days	after 11.9 days
5. Carb. diet	10	1	4	5	after 8.9 days	after 12.8 days

Discussion

In reviewing these results the following points are noted:—

(1) Under dietetic measures alone and without the help of any drug or serum, cases of bacillary dysentery were cured. Cases of toxic dysentery were also treated on the same lines, and apart from special measures aimed at combating collapse and dehydration, no other medication was administered. The majority of the toxic cases (73 per cent.) recovered.

(2) The majority of children given human milk did remarkably well. The mortality rate (5 per cent.) was definitely lower than in artificially-fed

infants (10 per cent.). The return of the stools to normal, however, did not take place rapidly and the gain in weight was slight or altogether lacking. Human milk, being rich in fat and lactose, is a poor antidyspeptic diet. Its poverty in protein and salts explains the defective gain in weight.

(3) With protein and buttermilks, the return of stools to normal was rapid and the gain in weight marked. These two milks are acidified and have a low fat and high protein and salt content. They are good antidyspeptic and antidystrophic diets.

(4) Apple diet gave satisfactory results. The therapeutic effects of apples and bananas are ascribed[18, 19] to pectin which probably acts by its buffer qualities, its adsorptive capacities and its ability to bind amines. The other constituents of apples and bananas, mainly malic acid, tannin and cellulose probably play a minor rôle. The high protein diet that follows accounts for the marked gain in weight and rapid return of stools to normal consistency.

(5) High carbohydrate diet was disappointing in its results. In the majority of cases diarrhoea persisted for a long time and gain in weight was lacking. One patient showed a false gain in weight by developing oedema. This oedema is mainly due to protein hunger (mehlhnährschaden)[20] and is accompanied by low plasma protein[21].

(6) Apart from the effect of the various diets on the general condition of the child, the stool picture and the weight curve, the bowel condition, as judged by the sigmoidoscopic appearances, was not materially influenced. The various modifications of diet failed to bring about rapid cure of the disease.

Conclusions

1. Bacillary dysentery is a self-limited disease in which recovery depends upon the development of immunity on the part of the body. Until such immunity has developed, the disease will continue its course irrespective of the character of the diet.

2. The underlying principles of treatment should be to choose a diet that maintains nutritution until the body has developed sufficient resistance to overcome the infection. The value of the various diets in maintaining this point has already been considered.

3. The sigmoidoscope can be safely used in infancy. It affords rapid and accurate means of diagnosis of dysenteric conditions. The course of the disease can be closely followed and the onset of final cure definitely established.

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ERYTHEMA MARGINATUM (RHEUMATICUM)

BY

C. BRUCE PERRY, M.D., F.R.C.P.

(Professor of Medicine, University of Bristol.)

Historical survey

At the International Medical Congress held in London in 1881 Barlow and Warner[2] read a paper on subcutaneous nodules in rheumatism and chorea in which they stated that of twenty-seven children with nodules ten had skin eruptions in eight of whom the rash was an erythema marginatum or papulatum. Barlow[3] later stressed the occasional occurrence of erythema marginatum at the onset of, or during the course of acute rheumatism.

In his classical monograph on the Rheumatic State in Childhood, Cheadle[5] classes an exudative erythema—erythema marginatum—as one of the specific manifestations of the rheumatic state in childhood, and he illustrates the typical rash by a drawing of a child who also showed a heavy crop of nodules. Cockayne[7], however, points out that the association between skin lesions and acute rheumatism was first described by Rayer in 1835. Poynton and Paine[18] described cutaneous manifestations of rheumatism which in many cases resembled tinea circinatum or erythema iris, and which may appear before the full picture of the disease has developed, during the attack, or as an almost solitary incident between definite attacks. Apart from these two papers little attention appears to have been paid to the condition recently until Lehndorff and Leiner[13] described the typical erythema marginatum under the title of erythema annulare. This may have been because erythema nodosum was for many years considered as a cutaneous manifestation of rheumatism, although it is interesting to note that Barlow was doubtful of this when he described the erythema marginatum in 1883. Since the paper by Lehndorff and Leiner, in which they stated that the eruption was a specific manifestation of acute rheumatism, several descriptions of the rash have appeared in the continental journals. (Chester and Schwartz[6], Lehndorff[12], Leichtentritt[14, 15], Walgren[20]), and to these authors has been given the credit for first describing the condition. In fact, Abt[1] appears to be the only author of recent years who has given Barlow and Cheadle credit for the original description. All of the authors quoted regarded the eruption as occurring only in rheumatic patients, but Swift[19] states that a similar rash may be seen in other infections. Goodall and Washbourn[11] describe an erythema marginatum or circinatum occurring in serum sickness and Davidson[8] suggested that the marginate erythema of serum sickness might be due to the albumin fraction

while urticaria and the morbilliform eruption were due to euglobulin and pseudo-globulin respectively. Debré[9] states that the rheumatic erythema annulare must be distinguished from the aberrant erythema marginata sometimes seen in serum sickness and from the rash of ' fifth disease.'

Many estimates of the frequency with which this eruption is found have been given. Leichtentritt[14] on a basis of ten cases states that it occurs in 62·5 per cent. of cases of rheumatic infection in childhood. Chester and Schwartz[6] describe it as occurring in ten cases out of twenty-one cases of acute rheumatism seen in an epidemic. Walgren[20] states that he has seen it in about 12 per cent. of cases (18 out of 146 children with acute rheumatism) and Lehndorff[12] estimates that it occurs in 10 per cent. of cases at the most. Abt[1] found that at the Spaulding School erythema was more common than nodules. Cockayne found rashes in 4·23 per cent. of children with chorea and in 4 per cent. of those with acute rheumatism. In the same series nodules occurred in 7 and 10 per cent. respectively. Maddox[17] in a study of 428 children with acute rheumatism in Sydney found sixty cases with rashes (14 per cent.); of these sixteen are described as ' morbilliform—erythema marginatum ' and thirty-three were ' unclassified.' It is probable that the majority of these were also erythema marginatum.

FIG. 1.—Showing the early stage of ' solid ' erythema just beginning to spread out.

Present series

During the past five years I have paid special attention to this eruption but it has never been seen except in patients with other evidence of rheumatic infection and it appears to be a specific rheumatic manifestation. In Bristol it is comparatively rare, and only thirteen cases have been seen, all children under the age of sixteen and it is less frequent than nodules. Characteristically the eruption starts as a solid erythema (fig. 1), little, if at all, raised. It gradually spreads out and as it does so the skin in the centre of the lesion returns to normal, thus forming the typical

spreading marginate or annular eruption (fig. 2). Where the spreading circles of rash meet they coalesce forming a larger ring (fig. 3). This suggests the possibility that the skin in the middle of the lesion might have become refractory to the irritant and thus could not respond again to the stimulus reaching it from a neighbouring eruption. In other words, that the rash was similar to the annular oedema described by Lewis and Zotterman[16] in a case of bacterial endocarditis. However, the skin inside the erythema has been tested in several cases and in all it reacted to light and heavy stroking, and to histamine, in exactly the same way as the skin outside. In only one case, in which the rash was very well marked, the inside edge of the erythema was slightly raised and oedematous. Carol and

FIG. 2.—Showing the later stage of the eruption—the typical 'erythema marginatum' or 'annulare.'

Krieken[1] performed a biopsy on one typical case and report that histologically the rash appeared to be an acute inflammation of the outer and middle layers of the cutis with a well-marked polymorphonuclear leucocytic infiltration. Debré, Lamy and Jammet[10] believe that the rash only develops in those severe cases of acute rheumatism with a streptococcus viridans bacteraemia. (These authors consider that there is no clear cut distinction between acute rheumatism and endocarditis lenta.)

The usual sites of its occurrence are on the front of the abdomen and on the front and back of the chest; it may develop on the limbs, but I have never seen it on the face.

TABLE.

	Age	Attacks of Rheumatism	Appearance of Rash	Duration of Rash	Other Rheumatic Manifestations	Sedimentation rate when rash present	Result
Stanley, F. ...	9	1	At end of attack	Persisted 10 months	Arthritis, Carditis and Nodules	?	Complete recovery
Dennis, T. ...	11 7/12	1	At onset one relapse of rash only	2 months	Carditis	?	,, ,,
June, H.	5 5/12	1	At onset	3 months	Arthritis and Carditis	?	Permanent cardiac lesion
Marjory, K. ...	6	2	At end of first attack	24 hours	Arthritis and Carditis	?	Death in relapse
Peter, D.	9 6/12	1	At end of attack	6 months	Arthritis and Carditis	Normal	Complete recovery
Robert, T. ...	11	2	After second attack	Few days	Carditis	Normal	Minimal cardiac signs persist
Douglas, W. ...	8 6/12	2	At onset second attack one relapse of rash in convalescence	Few days	Arthritis and Carditis	Slightly raised	Complete recovery
May, H.	11	2	In quiescent interval	—	Arthritis and Carditis	Normal	Permanent cardiac lesion
Albert, M. ...	15	1	In first attack	On and off 3 years	Arthritis, Carditis and Nodules	Raised and normal	Permanent cardiac lesion
Ellen, W.... ...	8	4	In each attack	2 days to 3 weeks	Chorea and Carditis	Raised	Death in relapse
Dennis, B. ...	12 3/12	5	Late in fifth attack	11 months	Arthritis and Carditis	Normal	Permanent cardiac lesion
Florence, H. ...	7	1	At onset and seven years after	2 weeks and 1 month	Arthritis and Carditis	Normal (in second attack)	Complete recovery
Gladys, P. ...	13 9/12	2	At onset of second attack	6 months +	Arthritis and Carditis	Raised	Still active

It may, and usually does, appear at the onset of an acute attack or relapse of rheumatism but it is frequently present when there are no other signs of active infection and when the sedimentation rate is normal. Once it has occurred it tends to come and go lasting from one or two days to months or years. In five of the present series of cases it was seen whenever the child was examined for from six months to three years after all other evidence of activity had disappeared (see table). This has been noted by others, and Walgren on account of this phenomenon has suggested that the

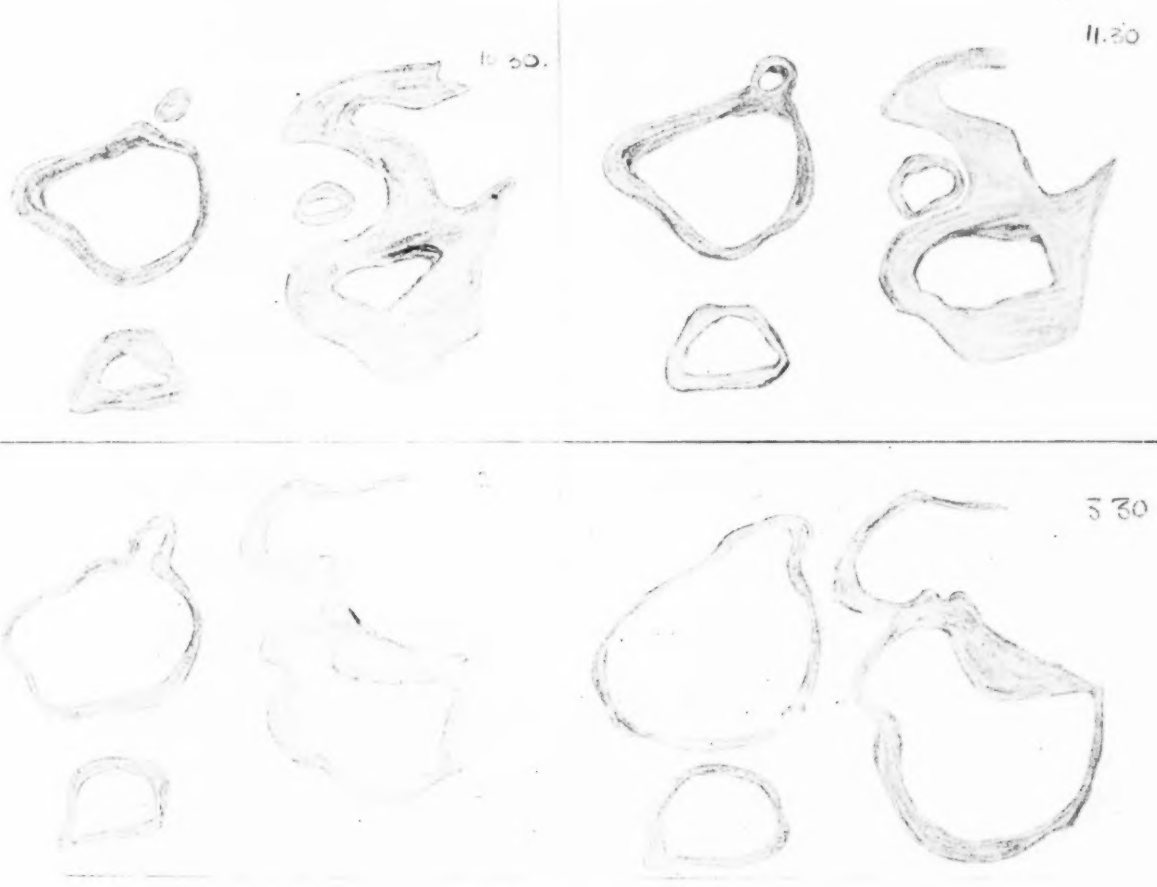

FIG. 3.—Tracings of the same area made at 10.30 a.m., 11.30 a.m, 2 p.m. and 3.30 p.m. on the same day, showing the spread of the rash and the way in which the circles fuse on meeting.

rash may be ' an angio-neurosis arising on a rheumatic allergic basis in certain highly susceptible individuals.' In one case of acute rheumatism with carditis running a polycyclic course the rash in the acute phase appeared to be most intense when the other manifestations were subsiding or were at a minimum. In only two patients was the rash present at the same time as nodules.

Although the rash may last for many months yet from these few cases it would appear that the development of the rash would tend to indicate a good prognosis as regards the actual rheumatic lesions since in four of the thirteen cases all abnormal cardiac physical signs have disappeared.

Summary

(1) Erythema marginatum is a specific manifestation of acute rheumatism.

(2) This eruption usually first appears at the onset of a rheumatic attack or relapse but may continue long afer all other evidence of rheumatic activity has disappeared.

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ACUTE MYELOID LEUKAEMIA IN ONE OF IDENTICAL TWINS

BY

C. E. KELLETT, M.D., M.R.C.P.
(The Royal Victoria Infirmary, Newcastle-on-Tyne.)

Joseph Needham[1] has recently observed that ' progress in science consists not so much of finding the right answers to certain definite and sensible questions, as of deciding what questions are sensible, and of making them definite.' In clinical medicine this is as a rule by no means easy, for cases occur in a haphazard manner in populations subjected to a variety of external influences which will not admit of more than partial investigation, and in the vast majority of such cases the ' control,' which is such an essential factor in all biological experimentation, is inevitably lacking. The following case of acute leukaemia has therefore seemed worth placing on record in so far as it occurred in a family who lived for generations in a sparsely populated moorland, who are of inbred stock, and moreover in one of a pair of identical twins. No new etiological theory has emerged from the study of this case, but it can be claimed that as a result of this and other similar cases many urgent questions now vague and conjectural will admit of a clearer definition.

Case record

Louie G., aged fourteen-and-a-half years, was admitted to the Royal Victoria Infirmary under Dr. George Hall on January 12, 1937. She is one of a pair of twins who came second in a family of five children, the oldest being a girl aged sixteen who lives with her grandmother, and the other two a boy of thirteen and a girl of seven. The twins were 3½ lb. each when born, and at one-and-a-half years both caught measles, the progress of the disease being the same in each of them. Shortly afterwards they both caught whooping cough and again the picture of the disease was similar. They remained well until they were eight years old when both had chicken pox, but this time Louie caught the infection in January and her twin sister not until April, though again the course of the disease was similar in the two. They remained well until last year when Leah had mumps in November and Louie a month later in December. For six months prior to this, however, Louie had been unwell; had complained of headaches and lost her appetite, had had fainting attacks and gradually lost colour. Three times prior to admission she had prolonged epistaxis. Her twin sister on the other hand remained well. The family have lived for several generations at Allendale, and for the past seven years have not been away from their home, which is on Lord Allendale's estate some ten minutes' walk from the small village of Carshields. Five weeks prior to admission Louie had however been sent to Allentown to live with her aunt in the hope that the change might benefit her.

TABLE 1.

DATE	RED BLOOD CELLS PER C.MM.	HAEMOGLOBIN PER CENT.	WHITE BLOOD CELLS PER C.MM.	PRIMORDIAL CELLS PER CENT.	PREMYELOCYTES PER CENT.	MYELOCYTES PER CENT.	METAMYELOCYTES PER CENT.	POLYMORPHS PER CENT.	LARGE LYMPHOCYTES PER CENT.	SMALL LYMPHOCYTES PER CENT.
13 i 37	950,000	35	7,500	90	3	1	1	5	—	—
18 i 37	850,000	28	19,860	95	2	1	—	2	—	—
19 i 37	Transfusion 12 oz blood	—	—	—	—	—	—	—	—	—
27 i 37	100,000	30	22,000	95	2	1	2	—	—	—
4 ii 37	700,000	28	60,600	96	1	1	2	—	—	—
15 ii 37	700,000	28	84,300	97	—	1	1	1	—	—
22 ii 37	660,000	22	116,000	97	—	1	—	2	—	—
27 ii 37	700,000	20	133,600	98	—	1	1	—	—	—

On admission she was found to be of good general physique but pale. She appeared recently to have been bleeding from a sore lip, but her mouth was clean. No purpuric haemorrhages were present, her spleen was not palpable, and she had no enlargement of her lymphatic glands. Her blood picture is summarized in table 1, and even at this stage was remarkable in so far that most of the white cells were exceedingly primitive and the red blood cells showed evidence of an equally gross disturbance.

Six days after admission she began to bleed extensively from the nose and seemed likely not to survive the night. She was given a blood transfusion of 12 ounces, and appeared for a time to have made a remarkable recovery, though, as shown in the table, her blood picture steadily became worse. At about this time the edge of her spleen was just palpable. She had moveover developed a small boil on the middle finger of her right hand, and following this the glands in her right axilla became enlarged and remained so. Her pulse rate, which had throughout been rapid, dropped for a time after the transfusion, as did her temperature, and for two or three weeks there was little change in her condition apart from a steady increase in the count of white cells. She then began to go rapidly downhill and her spleen became enormous, reaching down to well below the umbilicus and at this stage her parents decided to take her home in order that she might die there. She lived for a further week and a day, lying propped up in bed. Three days before her death she began to bleed from her nose again, and from that time on could only take cold water, which she took in large quantities. She complained bitterly of her head, and at times was unconscious. About two hours before she died all the pillows were removed from behind her and she lay down quite flat and appeared to have become unconscious, dying peacefully as if in her sleep. Vital staining of the white blood cells shortly before she died revealed that a considerable proportion of these cells were immature myelocytes.

Throughout this time Leah, her sister, enjoyed excellent health; from time to time she has been examined, and her blood picture has remained normal. The last count taken on April 28, 1937, was as follows: Red corpuscles, 5,200,000; haemoglobin, 85 per cent.; leucocytes, 5,600; of these 60 per cent. were polymorphs, 2 per cent. basophils, 10 per cent. large lymphocytes, 23 per cent. small lymphocytes and 2 per cent. monocytes.

Family record

As the photographs show, Louie strikingly resembled her twin sister Leah (fig. 1, A, B, C and D). They both wore glasses and their refractive errors were, as shown, virtually the same. A ' casual examination ' of their finger prints here reproduced (fig. 2) together with certain measurements can leave no doubt that they amply fulfil Stock's criteria, and should therefore be considered as being identical uni-ovular twins.

The family history can be traced back on the mother's side to her great grandparents. Her great grandmother at 79 is alive and well; her great grandfather died at 70 from a stroke. They had five children, of whom three are alive and well, and two, including the child's grandparent, dead, her grandfather having died of tuberculosis at the age of 41 and her grandmother also of tuberculosis at the age of 23. One of her great-aunts had twins, boys now aged 17. These and the twelve other members of this generation are alive and well. Her mother and her two uncles are alive and well, as are her own sisters and brothers. On the mother's side it has not been possible to discover any example either of leukaemia or, which is probably more significant, of malignant disease, and this would appear to be true of her father's si le of the family. Her paternal grandparents both died over

Fig. 1 A.—Patient Louie G.

Fig. 1 B.—Twin sister Leah G.

FIG. 1 C.—Louie G.

FIG. 1 D.—Leah G.

the age of 70. Her bachelor uncle is 49 and her spinster aunt is 47, and a married uncle has five children who are also alive and well as are also her own parents. It is interesting to note that Louie's great-aunt who had twins married her paternal grandmother's brother. Apart from this no

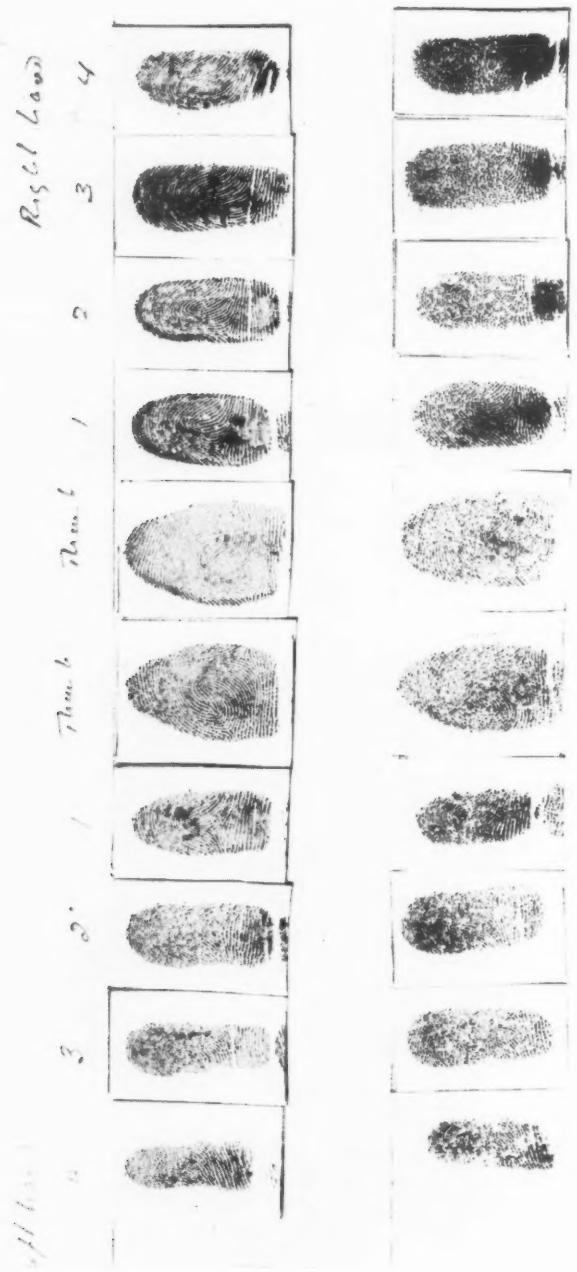

Fig. 2.—Top set of prints from Leah. Lower set of prints from Louie.

other inter-marriage appears to have taken place between the two families, though since they are Dales folk it is probable that the stock has interbred for many previous generations.

TABLE 2.

MEASUREMENTS OF TWINS.

	LOUIE	LEAH
Skull, length.	175.0 mm.	177.5 mm.
Skull, breadth.	147.5 mm.	146.0 mm.
Skull, circumference	530.0 mm.	532.5 mm.
Interpupillary distance.	52.5 mm.	52.5 m.m.
Refractive errors of eyes. As determined from their glasses.	R.E. —8.0/—1.0 45.	R.E. —8.0/—2.0 20.
	L.E. —8.0/—1.0 135.	L.E. —8.0/—2.0 180.

Colour of eyes and hair identical. Whorl of head hair both clockwise. Both right handed and both belonging to blood group 2.

Discussion

While nothing definite is at present known of the etiology of the acute leukaemias, and it is still doubtful whether these conditions should be regarded as neoplastic, certain hypotheses have from time to time been advanced which would seem to cover the whole possible etiological field. It has been suggested that the condition may virtually arise independently from external factors, as an expression of an inherited pre-disposition; or else alternatively that it arises as a result of some unknown external specific infection; or else again that it arises as a result of the inter-action of both these factors; or finally it is supposed that this condition represents the result of an abnormal inherited response to some common known external stimulus.

The evidence in favour of the first of these hypotheses is in the main based on experimental work carried out in mice. Slye's work[2] seemed clearly to prove that the genetic basis was a recessive Mendelian gene, but subsequent work by Richter and MacDowell[3] seems to have shown that while a hereditary factor is of paramount importance the exact method of the transmission is by no means clearly understood, yet in their strain ' from the 18th–23rd generation, about 90 per cent. (omitting doubtful cases) of all mice surviving more than six months developed leukaemia spontaneously.'

So far as work in man has been concerned obvious difficulties present themselves. Considerable intervals of time elapse between successive generations, and it is obviously impossible to obtain by methods of in-breeding a relatively homogenous strain such as the C58 employed by MacDowell and Richter in which inbreeding by brother and sister mating had been carried out for eighteen generations before the start of their investigation. Nevertheless, it is perhaps worth noting that while certain remarkable cancer pedigrees have been reported in man, such as those by Warthin[4] and Lockhart-Mummery[5], no such pedigrees have been reported in cases of leukaemia, and examples of familial or hereditary cases of leukaemia

are actually strikingly few. These cases, eleven in all, have recently been reviewed by Petri[6], and subsequently added to by Morawitz[7].

Another method of approach, however, does exist in man, in whom the difficulty of obtaining inbred strains can to some extent be overcome by the use of identical twins, as was noted by Galton[8] many years ago. Elsewhere[9] the writer has dwelt on the difficulties underlying the recognition of such twins and the pitfalls inherent in their use; while the whole field of twin pathology has been recently reviewed by Siemens[10], Margolis and Eisenstein[11], and Stransky[12].

While there is as yet no certain method of identifying identical twins, Louie and her twin sister fulfill all the criteria laid down for such twins by Stocks, and in the present state of knowledge it would appear impossible to consider them as being other than homozygous. If that is so it is apparent that the acute leukaemia which supervened in Louie could not be a result of the emergence of some purely hereditary factor but that some external factor common to one and not the other must have played some part in its emergence. It would seem furthermore that a greater significance must be attached to this case of twins in which only one of them had the condition than to the apparently only other pair reported by Dameschek[13] in which both of the twins died after one another at the age of fifty-six from a chronic lymphatic leukaemia, in so far as in such studies negative findings must of necessity be of greater significance than positive ones since twins are obviously affected simultaneously by a variety of infectious disorders in which hereditary predisposition may play no important rôle. It is, however, impossible at this stage to assert that this occurrence of acute leukaemia in one of identical twins implies that hereditary factors play no part in the etiology of the condition. Champlin[14], for instance, reports an example of twin brothers said to be alike in whom sarcoma of the testis developed in one at the age of twenty-four and in the other at the age of thirty-one. The first one had received a severe knock in the testis some years prior to the occurrence of the sarcoma, and it is not unreasonable therefore to suppose, as Macklin[15] suggests, that here the emergence of the condition had been accelerated by trauma and that had there been no such trauma a sarcoma might have supervened in both twins simultaneously; as did a fibro-adenoma of the breast in twins reported by Burkard[16], and an adeno-carcinoma of the uterus in twins reported by Croom[17]; so that twins indeed supply some of the strongest evidence in favour of the hereditary factor underlying neoplastic processes. It should be emphasized that so far as could be determined Louie and her sister had led identical lives and met the same people until the disease became manifest. Consideration therefore of this case does lead to the conclusion that the first of the etiological hypotheses suggested is untenable in this particular instance, but while there remains the hypothesis that the condition is due solely to some external factor or infection, and so far as this case goes some support is lent to this view, it is apparent that it is impossible on

this case alone to rule out the third hypothesis. This suggests that a leukaemia arises as a result of the interaction of both of these factors but while some believe that the external factor is a specific one there are many who appear to hold that this need not be so.

Poynton, Thursfield, and Paterson[18], who analyzed eighteen cases of leukaemia, incline to the belief that the solution of the problem lies rather in some peculiar reaction to infection than in the existence of some peculiar specific infective agent, and such cases have been reported by Isak Lundholm[19] who published a case of staphylococcal sepsis in a girl of three-and-a-half years that apparently developed into an acute lymphatic leukaemia, and Bonciu and Ionesco[20] who reported the case of a little girl with a haemolytic septicaemia and similar blood changes and discuss at length that conception of Sternberg ' pour qui la leucémie aiguë ne serait qu'une réaction biologique des organes hématopoïétiques provoquée par le streptocoque.' A number of related examples have also been recorded by Donath and Saxl[21]. Some years ago the writer[22] analyzed the mode of onset of forty cases of acute myeloid leukaemia and sixty cases of lymphatic leukaemia in childhood and was unable to find any real support in favour of this theory. In not less than three instances, however, an acute leukaemia was said to have come on following whooping cough, and in two instances following mumps. Both Louie and Leah had whooping cough at about the age two of these children are said to have had it and developed leukaemia, but despite the predisposition which must have been present neither of them seemed to develop anything approaching the leukaemic state. So much might, however, be said of any child who had had pertussis in infancy and subsequently developed a leukaemia. On the other hand, had it not been for the existence of a control it might have been argued in this case that the leukaemic picture had supervened as a result of an attack of mumps even though from her mother's story it seems quite clear that Louie was ill for several months before she contracted mumps. The complete absence of any such change in the blood picture of her sister Leah would seem to rule out this factor, and there can be little doubt that the accumulation of cases similar to these will ultimately dispel the rather vague widespread feeling referred to in the paper already quoted of Bonciu and Ionesco that relates the leukaemias to some sort of peculiar response to a common known infection.

The remaining hypothesis is one which postulates a specific infection. The experiments of Furth[23] and MacDowell[3] in transmission of experimental leukaemias in mice suggests that the susceptibility of the host is of the greatest importance. So far as these twins are concerned it must a priori be supposed that their susceptibility is the same. This would suggest that the infectivity of the specific etiological agent cannot be high. In the ordinary sense of the word there is indeed no real evidence of the infectivity of this condition. Mention has already been made of the low familial incidence, and the case reported by Obrastzow[24] of infection from patient to

nurse remains, as Baar and Stransky[28] remark, unique. Mothers with leukaemia have given birth to healthy children, and the solitary transfusion experiments of Schupfer[26] from man to man, as well as many experiments of injection into animals, remain negative. On the other hand the occurrence of disease is an exceptionally poor index of infection having occurred, though in this condition it is apparently the only one, for actual disease will occur only in susceptible people. In such circumstances one may argue that while the severity of the epidemic will depend on the numbers of such people and the virulence of the infection, the spread of the infection will be revealed only by the sporadic appearance of the disease. The four cases described by Aubertin and Grellety Bosviel[27] are therefore possibly of significance, in that they occurred within a few weeks of one another in a relatively restricted area, and with this may possibly be associated the fact that in every instance the leukaemia was exceedingly acute. The resemblance of these cases to the one here described and the relative isolation in which Louie and her family lived encouraged the belief that something might emerge from a study of any cases with which they may even indirectly have had contact.

Enquiries made by the writer, by the patient's family and by her own physician failed to reveal any possible source of such infection; on the other hand a search through the records of the Royal Victoria Infirmary for the past five years yielded information which is probably significant.

A local investigation

During the past five years sixty-three cases of leukaemia were admitted to the hospital, and during this period approximately thirty-two persons per million per year are reported as having died of the condition according to the Registrar-General's figures. In this condition the incidence rate must approximate closely to the mortality rate, and it is therefore possible to arrive at a rough estimate of the number of cases that are likely to have occurred in this area and of the proportion sent on to this hospital. Now the maximum population of this area from which the Royal Victoria Infirmary draws its patients is probably less than 1,750,000 persons (Northumberland 756,782; Durham—less Sunderland, Darlington and the Hartlepools–1,160,131), so that it would appear that a significant proportion of all cases of leukaemia occurring in this area pass through this institution. This population is from an epidemiological point of view conveniently distributed in the main within a few miles of Newcastle, thus constituting a large 'reservoir,' and then scattered in varying sized communities and at times extremly sparsely over a wide area.

In such circumstances if this condition be really due to some external infection as a study of these twins demanded then it might reasonably be hoped to demonstrate a rather constant emergence of this condition in a sporadic manner in the main reservoir and from time the appearance of the condition in virtually epidemic proportions in one or other of the outlying

communities, particularly if the outlying community be not too sparsely populated. Such a distribution on the other hand would be unlikely to arise if the condition were due to some other factor.

For the purposes of this investigation a point was chosen in an arbitrary manner approximately halfway between Newcastle and Sunderland, and a circle drawn around this point having a radius of eight miles. This circle included approximately 29,610 acres of the 1,291,978 acres of Northumberland and of 462,079 of the 746,096 persons living in the County at the time of the 1931 census, and 97,783 acres of the 649,420 acres of Durham and 711,010 of its 1,486,175 inhabitants; it is apparent that about half the population of the two counties live within this arbitrarily chosen rather restricted area. The communities without this area consist in the main of mining villages living under very similar conditions and agricultural communities, often very diffusely scattered, who are on the whole strictly comparable.

Of the sixty-three cases of leukaemia admitted from 1932-1936 inclusive, eleven were classified under the heading of acute myeloblastic leukaemia. Of these, five arose at approximately yearly intervals within the central area in an entirely sporadic manner at considerable distances from one another, the remaining six from without this area. In marked contrast to the five cases within the area these cases, with the exception of one case which occurred apparently sporadically at Tudhoe, Spennymoor, in 1935, a large mining village some twenty miles south of Newcastle, occurred under what, on analysis, appeared to be almost epidemic conditions, three at or near Ashington, a large mining village some twenty miles north of Newcastle and two west of Newcastle in the very area from which the case reported in the twin occurred. In so far however as the latter group are in a rural area, the Hexham R.D., which has a population of 21,306, an acreage of 196,812, and a density of 0·11 persons per acre, the inter-relation of the cases is less definite than at Ashington, where the density in the Hirst ward where the cases occurred for the most part is 29·0 persons per acre, the acreage being 676, and persons 19,623, that of Ashington as a whole being 9·7, the acreage being 3,309 and the population 29,418.

Of the twenty-five cases of chronic myeloid leukaemia fifteen occurred within the area and ten without; one of these occurred at Ashington at the time the epidemic began, and one again in 1936 within six miles of Louie, apart from these two, the cases appeared to arise sporadically, and no other cases appeared in these two particular ' epidemic areas.'

Of the thirteen cases of acute lymphatic leukaemia six occurred within the area and seven without; so far as they could be determined they arose in a sporadic manner; one case however of acute lymphatic leukaemia came from Ashington from the same street and at the same time as a case of acute myeloid luekaemia; no other case came from this area under the rest of the period under review. Of the fourteen cases of chronic lymphatic

leukaemia only four came from within the area and ten from without, one of these again coming from Ashington*; so far as could be determined these cases all arose in a sporadic manner.

So far as it goes this investigation into the hospital records proved more helpful than might have been anticipated, though it must be emphasized that none of the epidemiological data so ascertained have the clear cut quality of that derived from a study of the twins. This investigation not only supplied a possible source for Louie's infection but also some slender support for the explanation tentatively advanced to the issues her case had so clearly raised. For H. C., a young man of twenty-three, who lived at Slaley in the same sparsely populated area as Louie some fifteen miles away from her and died of an acute myeloid leukaemia in Professor Hume's wards on November 17, 1936, had been ill since April, and being a motor driver had the relatively wide range of action essential if he were to act as a vector in an area with a density of 0·11 persons per acre, while the concentration of cases such as occurred at Ashington lent some support for the contention that Louie's condition had arisen from some external infection, widespread possibly, but since her identical twin escaped, of such low infectivity as to suggest the intervention of a second factor such as an insect vector.

Summary

A case of acute myeloid leukaemia is described in one of identical twins. It is pointed out that this case raises certain clear cut issues that can be best met by the assumption that her condition arose as a result of the action of some external factor, specific, but of low infectivity. An analysis of the cases of leukaemia admitted into the Royal Victoria Infirmary over the past five years yielded information that tended to support such an assumption.

Thanks are due to Dr. George Hall for his permission to publish details of this case admitted under his care, and to the Honorary Staff and Department of Pathology of the hospital for permission to make use of their material.

Appendix

SUMMARY OF CASES OF LEUKAEMIA ADMITTED FROM ASHINGTON AND ITS VICINITY INTO THE ROYAL VICTORIA INFIRMARY FROM 1932 TO 1936 INCLUSIVE

H. D., age 19, from Ashington, was admitted on August 31, 1932, with a history of frequent epistaxis and weakness since March of that year, which had been relieved in May on the occasion of her first admission by deep x-ray therapy, under Dr. Parkin. Her spleen and lymph glands were enlarged, she had 2,400,000 R.B.C. and 150,000 W.B.C. per c.mm., and a differential count of 17·5 per cent. myeloblasts, 24·5 per cent. pre-myelocytes, 7 per cent. neutrophil myelocytes, 7 per cent. neutrophil meta-myelocytes,

* This patient, A.M., appears on re-examination of her autopsy preparations to have been an undoubted case of sub-acute myeloid leukaemia.

19·5 per cent. polymorphs, 12·5 per cent. basophils, 1 per cent. eosinophils, 9.5 per cent. lymphocytes, 1·5 per cent. monocytes. She died September 14, 1932, and autopsy revealed findings characteristic of a sub-acute myeloid leukaemia. (Differential count and autopsy done by Professor Bernard Shaw.)

G. P., age 43, from Ashington, was admitted December 5, 1932, under Dr. Drummond with a history of sudden extensive bruising of his left leg and right arm since November 16, 1932. He had 1,540,000 R.B.C. and 30,000 W.B.C. per c.mm., and of these 99 per cent. were myeloblasts and pre-myelocytes. He died December 19, 1932, and autopsy revealed findings characteristic of an acute myeloblastic leukaemia. (Differential count and autopsy done by Professor Bernard Shaw.)

J.W.L., age 16, from Ashington, was admitted January 13, 1933, under Dr. Hall with a history of prolonged haemorrhage following tooth extraction on January 1, 1933. A blood film ' resembled a bone marrow film,' and the immature cells were thought to be lymphoblasts. He died January 16, 1933, and the autopsy revealed findings typical of an acute leukaemia. (Autopsy by Professor Bernard Shaw; microscopic preparations not made.)

J. Q., age 34, from Ashington, was admitted under Dr. Drummond, January 7, 1934. He gave a three weeks' history of ' lumps and rheumatics down the left side.' His spleen was enlarged to his umbilicus, he had 2,500,000 R.B.C. and 400,000 W.B.C. per c.mm. The blood film was typical of a myeloid leukaemia. He died January 18, 1934, there was no autopsy.

A. M., age 41, from Ashington, was admitted under Professor Hume, July 15, 1935. She complained of weakness since Christmas, 1934, and of prolonged bleeding following the extraction of some teeth a month prior to admission. Petechiae were present, the lymph glands were not enlarged, the spleen not felt. She had 35,000 W.B.C. per c.mm. of which the great majority were very primitive. These were thought to be lymphoblasts, a subsequent review of the material obtained at autopsy (she died August 9, 1935), by Dr. J. G. Thomson, revealed the presence of a number of myelocytes and it would appear almost certain this was a case of sub-acute myelogenous leukaemia.

L. S., age 44, from a small village 10 miles north of Ashington, was admitted September 10, 1936, under Dr. Nattrass. She had been out of sorts for one year, and had had ready bruising and pallor for about two months. Her spleen was found to be slightly enlarged; she had 1,650,000 R.B.C. and 3,600 W.B.C. per c.mm., of these 75 per cent. were classed as primordial, 4 per cent. as myeloblasts, 6 per cent. as meta-myelocytes, 6 per cent. as polymorphs, 1 per cent. as monocytes, 3 per cent as lymphocytes and 1 per cent. as unclassified. She had three transfusions and died about fourteen days after returning home. (Differential count by Dr. J. G. Thomson.)

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THE PROGNOSIS IN RHEUMATOID ARTHRITIS IN CHILDHOOD

BY

THOMAS COLVER, M.B., M.R.C.P.

(From the Hospital for Sick Children, Great Ormond Street.)

Chronic polyarthritis in childhood is a disease of considerable frequency. In the medical wards of the Hospital for Sick Children, Great Ormond Street, sixty-nine cases have been treated since the war. There are additional out-patient cases which are not admitted to the wards and it is estimated that a new case may be seen at the hospital every twelve weeks.

In the wards the clinical picture of the acute phase is familiar, but apart from certain cases with early recovery the end results are seldom seen, so prolonged is the course of the disease. The institutions for chronic rheumatoid arthritis collect the most severely crippled but these form a minority. The fairest assessment of prognosis is attained by a follow-up enquiry of a consecutive hospital series and for this purpose the post-war cases have been taken.

The cases under review

The series of sixty-nine is depicted in fig. 1 where the cases are arranged according to the age of onset. Two cases are seen to have begun in the first year of life, fourteen cases in the third year with a maximum incidence in the pre-school period between two and five years. The sex incidence is also indicated. Sixty per cent. of the patients were girls.

Follow-up results. The results of the follow-up enquiry are shown in fig. 2. Enquiries were successful in forty-nine cases (twenty cases were untraced). Of these, twelve are known to have died, eighteen are still active and nineteen are quiescent. The criteria of quiescence have been an absence of joint pain and tenderness for a period of not less than two years, and a blood sedimentation rate within normal limits. In no instance have symptoms recurred after a quiescent period of eighteen months.

The fatal cases. A recognition of the considerable mortality was the first finding of importance (fig. 2). Twelve of the patients followed have died and in each case before reaching adult age. Each fatal case had first developed the condition under five years of age and with one exception each one had died within three years of the onset. The disease is thus most dangerous in the acute stages in the young children.

Figure 1 shows that forty-two of the cases developed symptoms in the first five years of life. Of these, twelve are dead—a mortality of nearly thirty per cent. at this period. The disease is thus most fatal in the years when it is most frequent.

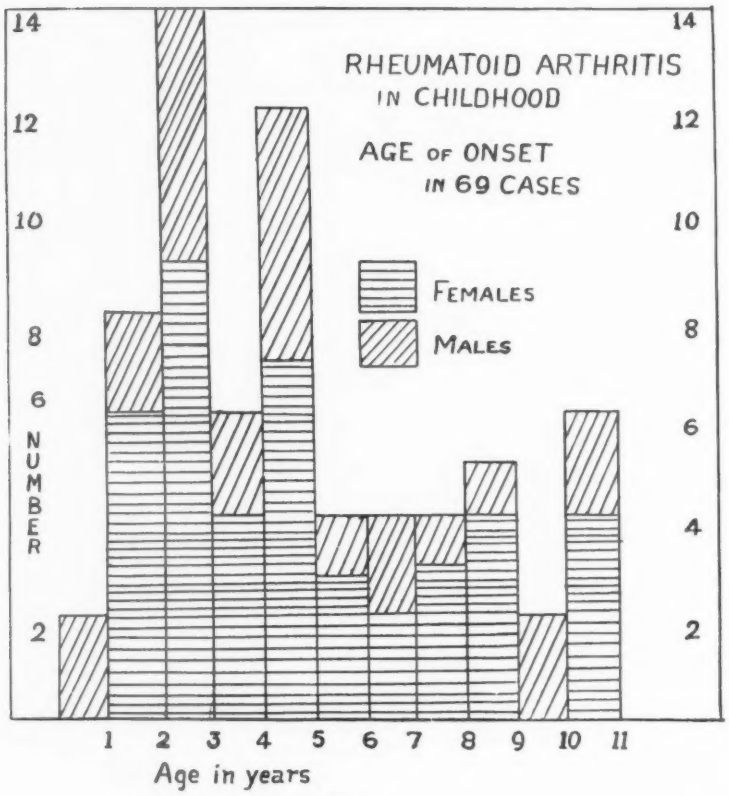
RHEUMATOID ARTHRITIS
IN CHILDHOOD
AGE OF ONSET
IN 69 CASES
FEMALES
MALES
NUMBER
14
12
10
8
6
4
2
1 2 3 4 5 6 7 8 9 10 11
Age in years

FIG. 1.

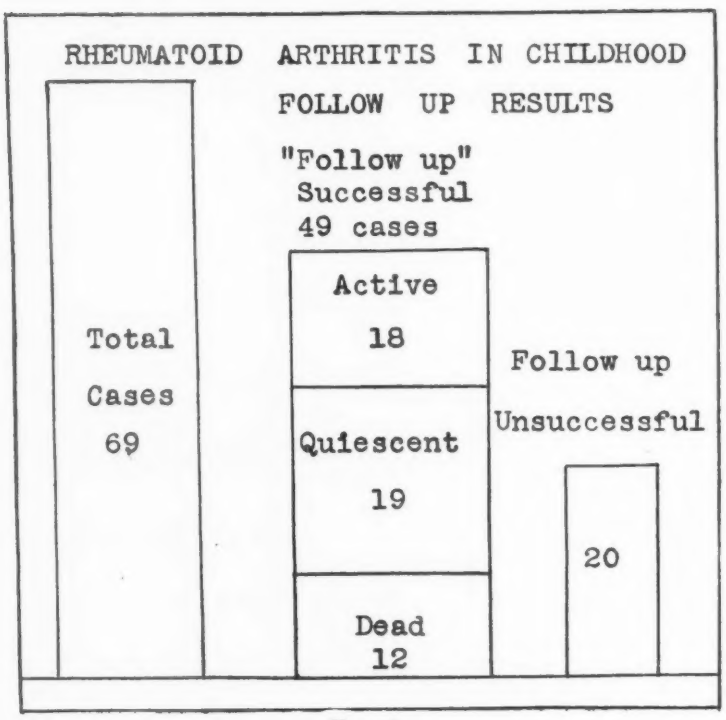
RHEUMATOID ARTHRITIS IN CHILDHOOD
FOLLOW UP RESULTS
Total
Cases
69
"Follow up"
Successful
49 cases
Active
18
Quiescent
19
Dead
12
Follow up
Unsuccessful
20

FIG. 2.

When however, the disease begins after the age of five the prognosis as regards life is good. There is no record of the death of any such patient. Again if any patient (even the youngest) survives the first three years the prognosis as regards survival is good.

CAUSE OF DEATH IN THE FATAL CASES. Five patients died in hospital. Autopsies were performed in four of these. In all cases there was a progressive emaciation and anaemia, the patient gradually being reduced to an almost prostrate condition. In two cases there was a terminal streptococcal septicaemia (haemolytic), in one a large renal calculus and heavy urinary infection. A fourth showed advanced amyloid disease and extreme pericardial adhesions. In the fifth the autopsy revealed no finding of note apart from extreme emaciation and moderate pericardial adhesions. Pneumonia has been cited as the cause of death in most of the cases that died elsewhere.

The quiescent cases. Nineteen of the series are now quiescent. They have no pain and have lost the emaciation and anaemia characteristic of the active stages. A proportion of them show a varying amount of crippling, but when examining these older patients one was impressed by the frequency

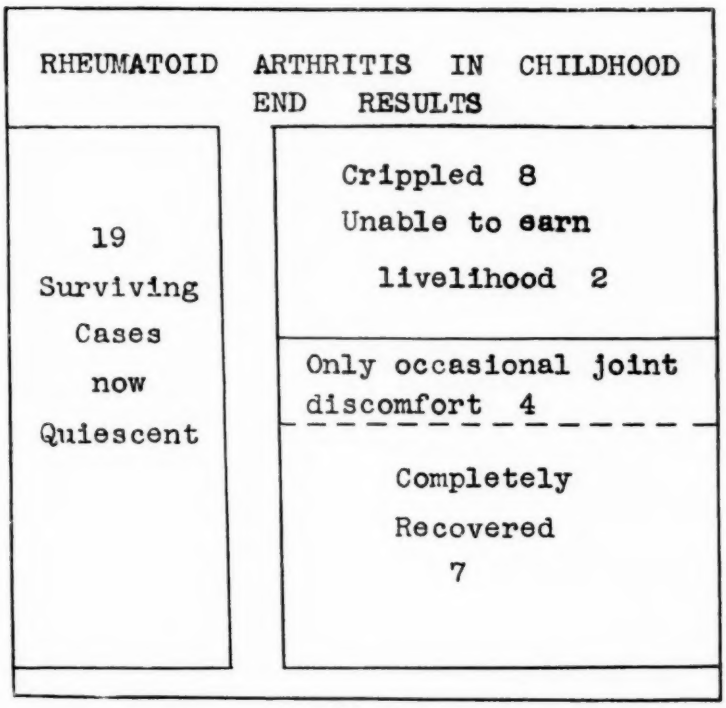

FIG. 3.

of complete recovery and by the relative infrequency of gross crippling. Crippling when it occurred was usually confined to two, three or four joints, the elbows and wrists being most frequently affected.

The details of these older patients are indicated in fig. 3. With two exceptions every patient can earn a livelihood. With one exception every patient can walk. Seven of the nineteen have completely recovered and a further four patients have recovered to all intents and purposes but full passive movement in one or two joints occasions slight discomfort. Eight old cases show some crippling but in only two of these is the ability to earn

a livelihood lost. Of the patients earning a livelihood the most severely incapacitated has limited movement in four joints. One elbow and one finger are ankylosed in flexion and there is partial limitation in both wrists.

FIG. 4.

(By courtesy of Dr. D. Paterson.)

Rheumatoid arthritis in infancy. The youngest case in the series. Symptoms began at six weeks of age and death occurred at nine months.

The duration of activity and its influence on the prognosis. Thirty-seven surviving cases have been examined; these include the active and quiescent cases indicated in fig. 2 and in no case has the duration of activity exceeded seven years. The disease thus appears to be self limited and in a given case one feels justified in predicting the cessation of activity within a maximum period.

In the nineteen quiescent cases the average period of activity proved to be nearly five years. The duration of the active phase is one of the most important factors in estimating the prognosis and apparently three years of activity is the critical period. If after three years the disease is active the risk of a fatal outcome is negligible but the chance of complete

FIG. 5A.

FIG. 5B.

(By courtesy of Dr. R. Hutchison.)

Rheumatoid arthritis in childhood. At this period the patient was five years of age. The disease was active for three years and was followed by complete recovery. (See Fig. 6 A and B).

recovery of function has almost disappeared. Eleven of the twelve deaths occurred within the first three years when constitutional upset is most severe. In the cases which completely recovered the disease ran a relatively short course, never longer than three years (twenty months was the shortest duration) and the end results also show that no case active for more than three years has completely recovered.

The treatment of foci of infection

Exacerbations of the disease are frequently related to infections, particularly of the naso-pharynx. Results after the treatment of septic foci have however been discouraging. So prolonged is the disease and so great the wish to leave no stone unturned that operations for the removal of possible foci of

FIG. 6A.

FIG. 6B.

infection have been frequent, but there is little suggestion on analyzing the results that the prognosis has been improved by these procedures. These patients in their lowered state of health readily develop secondary infection which must not be given a causative rôle. In seven selected cases however

the relation of definite focal sepsis to the onset of symptoms was so close that a special significance was difficult to refute.

In the first, symptoms began a few days after the removal of a grossly infected and gangrenous appendix; twelve months later exacerbations of the arthritis are still occurring. In one case symptoms began four days after the extraction of a carious tooth. There was an associated alveolar abscess. The subsequent extraction of a similarly infected tooth was followed by an exacerbation of symptoms. The active stage of the disease lasted two-and-a-half years. The patient is now symptom free. Recovery will probably be complete. In three cases the patients before the onset of symptoms presented that gross type of dental caries in which all the teeth are eroded almost to the gums. The teeth were removed in each case. One patient eventually died at the height of the disease eighteen months after the onset. In the second the disease is still active after three-and-a-half years. The third has not been traced. In two cases symptoms followed severe tonsillitis. Recurrence of the tonsillitis was followed in each case by exacerbations and tonsil enucleations were performed. One patient died after two-and-a-half years. The other suffered remissions for three years and then recovered. Even in these selected cases it is therefore difficult to draw definite conclusions.

With regard to the seven patients who recovered, in four no focus of infection was demonstrated, in two the tonsils, and in one carious teeth were incriminated and removed.

Cardiac complications

Similarities between this disease and acute rheumatic fever raise the possibility of cardiac complications. In none of the old cases however was it possible to demonstrate a valvular lesion. It should be mentioned that R. Hutchison observed in one of his patients (included in this series) the development of a mid-diastolic murmur. This case was not traced in the recent follow-up enquiry. Adherent pericardium, on the other hand, is a recognized complication and was found in two of the autopsies and one of the surviving patients.

Associated glandular enlargement

Many of the cases surveyed showed marked glandular enlargement in the active stages (Still type), the axillary and cervical glands frequently being visible on inspection and the spleen sometimes extending to the umbilical level. This associated lymphoid hyperplasia appears to have no influence on the prognosis. Its presence or absence is determined by the age of onset. In cases beginning in the first four years of life lymphoid hyperplasia is rather the rule than the exception (table 1). In the older age groups it is progressively rarer. There is no period in life, however, when the onset of rheumatoid arthritis may not be associated with glandular enlargement.

TABLE 1.

THE INCIDENCE OF GLANDULAR ENLARGEMENT IN CHRONIC POLYARTHRITIS IN CHILDHOOD.

AGE GROUP.	NUMBER.	NUMBER SHOWING GLANDULAR ENLARGEMENT.	PER CENT.
Under 4 years	31	25	80
4 to 12 years	34	11	33

Summary

(1) In an effort to estimate the prognosis in chronic polyarthritis in childhood a consecutive series of sixty-nine patients have been surveyed and follow-up enquiries pursued.

(2) The disease appears to be be self limited, the average period of activity being nearly five years.

(3) In the pre-school period the incidence of the disease is highest and the mortality approaches thirty per cent. A fatal outcome is rare when the disease begins in the second half of childhood.

(4) The deaths occur in the first three years of activity. If this period is survived the danger to life is small.

(5) Only a rough estimation of the recovery rate can be deduced. Approximately one in four recover completely. Complete recovery is limited to those cases in which the disease becomes quiescent within three years.

(6) Very gross crippling is uncommon. Surviving cases can usually earn a livelihood.

Thanks are due to the medical staff of the Hospital for Sick Children for the facilities to make this enquiry and to Dr. Donald Paterson for valuable assistance.

BRITISH PAEDIATRIC ASSOCIATION.

PROCEEDINGS OF THE TENTH ANNUAL GENERAL MEETING.

The Tenth Annual General Meeting was held at the Old England Lake Hotel, Windermere, on Friday and Saturday, May 7th and 8th, 1937.

First Session (May 7th, 10 a.m.)

Business Proceedings : The President, Dr. Leonard Findlay (London), was in the Chair, and there were present 55 members.

The Minutes of the last Meeting were read and approved.

The following Officers, and Honorary, Corresponding and Ordinary Members were elected :—

President : 1937-38, Dr. J. Wilkie Scott (Nottingham).

Secretary : Dr. A. G. Maitland-Jones (re-elected).

Treasurer : Dr. Donald Paterson (London), in place of Dr. H. Morley Fletcher.

Representative for London : Dr. Charles Harris, in place of Dr. Donald Paterson.

Representatives for Provinces : Dr. J. M. Smellie (Birmingham) and Professor C. Wilfred Vining (Leeds), in place of Dr. Hugh Ashby and Dr. Norman Capon.

Honorary Member : Professor A. E. Naish (Past President).

Corresponding Members : Professor E. A. Park (U.S.A.) and Professor A. Wallgren (Sweden).

Ordinary Members : Dr. R. W. Brookfield (Liverpool), Dr. W. W. Payne (London) and Dr. E. R. C. Walker (Aberdeen).

The Treasurer's Report was received and adopted.

A Vote of Thanks to Dr. Morley Fletcher for his devoted work as Treasurer of the Association for the preceding ten years was proposed by the President and seconded by Dr. Donald Paterson. This was agreed to with acclamation.

The Report of the Joint Committee set up to consider the proposed standard definition of prematurity was then considered. After some discussion the adoption of this Report was proposed by Dr. Capon, seconded by Dr. Sheldon, and carried unanimously.

The President addressed the Meeting on the need for all members of the British Paediatric Association to give their fullest support to the *Archives of Disease in Childhood*. After Dr. Charles Harris had outlined the future policy governing publication of the *Archives* a discussion took place, and it was agreed that every member should do his utmost for the well-being of this Journal.

The place of meeting for next year was then discussed.

Scientific Proceedings :

1. Professor E. Gorter (Holland), opened a discussion on Nutritive Food Requirements during the first year of life as set out in the League of Nations Memorandum, C.H./C.E. Alim. Nour. /6 (1), of December 12th, 1936. He emphasized the following points in the memorandum :—

(1) Calorie requirement. It was decided that the following represent the average number of calories necessary for infants of different ages :—

110 per kgm. first quarter of life.
100 per kgm. second quarter of life.
90 per kgm. second six months.

Fluctuations of 10 per cent. above and below these averages are considered as normal. The criticism that the needs of every child are different is answered by the addition that the number of calories—and this applies to other matters as well—should be adjusted to the individual needs of the child.

(2) Protein requirement. The amount of protein of 2 grammes per kgm. for breast-fed children corresponds to the number of calories and a protein content of breast milk of 1·25 per cent. For bottle-fed children the figure should be somewhat higher. The average of 3 grammes corresponds to a feeding of 2/3 milk and 1/3 of a 10 per cent. sugar solution given in an amount of 100 calories per kgm. Variations here are higher as can easily be seen by the comparison of the equally good results with diluted milk formulae and with buttermilk.

(3) Duration of exclusive milk-feeding. Exclusive milk-feeding should not be continued after the age of six months, because from this age other food substances are necessary for the maintenance of health.

(4) The total milk intake should not exceed 750 or 800 grammes. In different countries reduction of this amount after six months is advocated, as other food should be given and the total requirement of 90 calories per kgm. must not be exceeded.

(5) The daily requirement of vitamin C from the age of 3 months is estimated as 5 mgm. ascorbic acid, equivalent to 10 c.c. orange juice. This number is in excess of the daily excretion of 1-3 mgm. vitamin C in a healthy breast-fed child, who is saturated with regard to this vitamin.

(6) The daily requirement of vitamin D from the age of three months is 1/8000 mgm. of the crystalline preparation. This corresponds to 6 c.c. of cod liver oil of the American pharmacopoeia or to 500 international units. This figure is derived from the study of the incidence of rickets in a group of children seen at an infant welfare centre who received different amounts of vitamin D during the winter months.

This discussion was continued by Prof. G. B. Fleming, Dr. R. Jewesbury, Prof. C. W. Vining, Dr. N. Morris, Dr. J. F. Ward, Dr. W. R. F. Collis, Dr. A. G. Maitland Jones, Dr. J. C. Spence, Prof. L. G. Parsons, and Dr. L. Findlay.

2. Dr. J. V. C. Braithwaite (Leicester): 'The treatment of infantile pyloric stenosis by eumydrine.' Twenty-two patients with infantile pyloric stenosis were treated by giving them 5 c.c. of 1 in 10,000 solution of eumydrine (atrophine methyl nitrate) half an hour before feeds. All patients showed visible gastric peristalsis, projectile vomiting, and constipation, and in fourteen a palpable pyloric tumour was present. In all but one of the eight cases without a palpable tumour the diagnosis was confirmed radiologically. The technique advised by Svengaard was followed. Some of the patients had ammon. chlor. gr. ii t.d.s. to overcome alkalosis. Fifteen or 68 per cent. of the patients were bottle fed. Three patients were treated in a private hospital, two in a municipal hospital, and seventeen in a voluntary hospital. Four patients died. These were all in the Children's Hospital, and two deaths were due to a ward infection after the pyloric stenosis had apparently been cured. One patient died suddenly while feeding at the breast, and the other was a premature baby already infected at the time of admission. The three private cases and three out of four patients nursed in cubicles in the Children's Hospital all did well. Nine out of thirteen cases nursed in the open ward showed signs of enteral or parenteral infection. In four cases eumydrine apparently did not work, and they were subsequently cured surgically. In these patients the treatment was not persisted in for more than a few days.

3. Dr. H. L. Wallace (Edinburgh): 'Condensed milk for habitual vomiting in infancy.' The ages of the infants concerned ranged from three weeks to four months and all had been artificially fed, either from birth or from shortly after birth. There was a striking similarity of symptoms in all the cases, the outstanding feature being persistent vomiting occurring after nearly every feed. Another symptom common to all cases was marked restlessness and irritability, giving the impression of a state of chronic unhappiness. Apart from a slight tendency to constipation,

the stools were normal and there were no signs of intestinal indigestion. The real interest in connection with these infants lay in their failure to respond to ordinary dietetic treatment. Such measures as skimmed milk, diluted whole milk with added sugar, acidified milk, powdered milk and thickened feeds failed completely to control vomiting—the weights remaining stationary, or actually falling, despite a comparatively large caloric intake. As a last resource sweetened condensed milk was offered to these infants and the effect was both striking and immediate—the vomiting ceased, the weights increased steadily and the infants became placid and contented. The reason for this dramatic improvement is not easy to explain, since the caloric value of the condensed milk feeds was, in most cases, considerably less than the previous feeds and in one or two instances was appreciably below the normal requirements. It is suggested that the effect was ' psychological ' in these cases rather than physical, since the infants appeared to find the condensed milk pleasing and satisfying and as a result ceased to be restless and irritable and did not vomit. Vomiting in the absence of other signs of gastro-intestinal disorder, as occurred in these cases, may be in the nature of a habit-spasm occurring in a hungry, unhappy infant, and if this state of mind can be allayed by the giving of a feed which is both pleasing in taste and satisfying to the infant concerned the vicious circle is broken and the vomiting ceases.

4. Dr. F. J. Ford (Glasgow): ' Von Gierke's disease in several members of one family.' A family was reported, several members of which showed hepatomegaly. The course of the clinical observations together with the biochemical findings favoured the diagnosis of von Gierke's disease. There was a history suggestive of a hereditary occurrence of enlarged liver. One child improved rapidly after being given thyroid, and in another some evidence was found for suspecting a pituitary deficiency. The detailed account of this family will be published in the near future.

5. Dr. A. Moncrieff (London) and Dr. L. E. H. Whitby (introduced by Dr. A. Moncrieff): ' Purpura in the new-born.' Examples were quoted of toxic, mechanical and thrombocytopenic purpura in the new-born babies with special reference to the last-named. A full-term baby, born of healthy parents, was covered with purpuric spots and bruises at birth and had also bleeding into the mucous membrane of the palate. Blood examination showed complete absence of platelets in stained films with prolonged bleeding and clotting times. An intramuscular injection of 10 c.c. of father's whole blood was given and except for slight epistaxis on the fourth day of life there was no fresh bleeding. The platelet count, estimated as ' less than 5,000 per c.mm.' at birth, rose to 25,000 per c.mm. by the end of a month and to 350,000 per c.mm. by the end of a further six weeks with a corresponding decrease in the bleeding times. The spleen has never been palpable and the child appears to be making excellent progress. The relationship of this thrombocytopenic purpura to the haemorrhagic diathesis of infants was discussed and also the eventual prognosis—would the condition recur? Dr. Whitby commented more especially upon the normal platelet count of the new-born which, in his own experience and that of others had been of the order of 350,000 per c.mm. He considered the case belonged to the class of essential thrombocytopenias though the earliest hitherto recorded case had been in an infant of 4½ months (Greenwald 1927). The prolonged coagulation time was unusual but this abnormality had been the first to disappear.

6. Dr. Pearse Williams and Dr. K. H. Tallerman (London): ' Two cases of influenzal meningitis with recovery.' Two cases of influenzal meningitis were reported, one child being two-and-a-half years old and the other nine months. Both children made a complete recovery after treatment by repeated lumbar puncture. In each case the H. influenzae was cultured from the cerebro-spinal fluid. Reference was made to the recent use in America and Canada of specific serum. This serum being bactericidal in its action is mixed with fresh human serum to provide complement, the proportions used being seven parts of the specific serum to three parts of the fresh human serum. It is given both intravenously and intrathecally.

Figures as to the incidence rate of this disease and its mortality were also tabulated and discussed.

Paddington Green Children's Hospital. Four cases with two deaths.
London Hospital. Ten cases all of whom died.
(All these in the ten year period, 1927 to 1936.)
St. Louis Children's Hospital, U.S.A., 54 cases, 1918 to 1936.
Toronto Children's Hospital, Canada, 106 cases, 1919 to 1936.

In prognosis the age factor was of paramount importance, as mortality under the age of two years was higher than in those over the age of two years.

St. Louis Hospital cases, death rate over two years—83·3 per cent.
under two years—97·6 per cent.

Wilkes-Weiss had collected five hundred cases from the literature which have been tabulated in similar groups.

Death rate over two years—79·5 per cent.
Death rate under two years—97·6 per cent.

Workers in Toronto reported a fall in death rate from 98 per cent. to 72 per cent. after the introduction of specific serum therapy, but did not give their cases in age groups. Dr. Pearse Williams and Dr. Tallerman suggested that in collecting statistics and in determining the value of specific serum therapy, cases should be grouped in two series by all workers, viz. those under two years and those over two years. They felt that the fall in mortality reported to follow the use of specific serum might be attributable to the age factor.

Second Session (May 7th, 9 p.m.).

7. A discussion was held on the examination for the 'Diploma in Child Health.' This was opened by Dr. H. Morley Fletcher (London), Prof. L. G. Parsons (Birmingham) and Dr. H. T. Ashby (Manchester). The following took part: Dr. A. Moncrieff, Dr. R. Hutchison, Dr. J. F. Ward, Dr. E. A. Cockayne, Dr. J. D'Ewart, Dr. A. Ogilvie, Dr. W. R. F. Collis, Dr. A. G. Watkins, Dr. L. Findlay (President) and Dr. A. G. Maitland Jones (Hon. Secretary).

Third Session (May 8th, 10.30 a.m.).

8. Prof. A. E. Naish (Sheffield): 'New treatment of haemophilia.' A brief account was given of the steps that led Dr. Timperley to the discovery that the injection of an incubation product of egg-white and potassium bromide had a haemostatic effect on the external and internal bleeding of haemophilics. The active principle had not yet been obtained in a state of chemical purity, and the end-products of different batches of material were not consistently of the same potency, nor were the keeping properties the same. This matter was receiving attention, but until a stable and consistent product had been obtained it was necessary when treating a haemophilic patient to be armed with materia! which had been recently tested on a known haemophilic. This of course limited at present its general usefulness. The positive points which were most convincing with regard to its therapeutic effect were (1) the remarkable effect on the clotting time; (2) the rapid visible effect of an injection on an external bleeding surface; (3) the disappearance of a previous tendency to haematomata from injury after a course of injections; and (4) the freedom from haemarthrosis, and the consequent improvement in health and working capacity of five haemophilics who have been kept on maintenance dosage for a year or longer. One of these five patients was knocked down by a motor lorry and lost an area of skin over his left knee of about 4 inches in diameter. Shock was severe for about twenty-four hours, but bruising was no more than might be expected in a normal person, and the denuded area showed but little bleeding.

9. Prof. C. B. Perry (Bristol): 'Erythema marginatum (rheumaticum)
(see p. 233).

10. Dr. J. H. Hutchison (Glasgow), introduced by Dr. S. Graham: 'Observations on the retention of iron.' A series of iron-balance studies have been conducted on twelve in-patients at the Royal Hospital for Sick Children. These experiments have been carried out over long periods on each patient, comprising in some instances as many as twenty weekly periods on metabolism. The results of such experiments on two typical cases of this series were presented. The first case was a girl, aged 10½ years, suffering from chorea minor. Inorganic iron in the form of ferrous sulphate was administered in doses of 4 grammes per week for five weeks and 8 grammes per week for four weeks. This girl, who presented throughout a normal blood picture, retained from 72-87 per cent. of the total iron intake per period on 4 gramme doses, and from 27-76 per cent of the intake on 8 gramme doses. On discontinuance of iron administration some re-excretion took place. Over the length of time of this experiment, i.e., until a positive iron-balance had been regained after stopping the iron administration, this girl retained in the body 3·5 grammes of iron. The second case was a boy, aged 3 years, suffering from profound nutritional anaemia. An iron-balance study was conducted while under treatment with 4 grammes of ferrous sulphate per week. Between the first weekly period on metabolism, and the eighth period, 2,896 milligrammes of iron were retained and stored in the body, which had it been fully utilized for haemoglobin building, would have resulted in a rise of 13 per cent. haemoglobin per day. The actual rise of 55 per cent. in the haemoglobin (1 per cent. per day), during that period represented the addition of only 259 milligrammes of iron to the circulation. It would seem that there is at present no satisfactory explanation why such large doses saturating the tissues with iron are more effective than smaller doses only supplying enough iron for haemoglobin building. Various theories were discussed and an original one suggested.

11. Dr. J. C. Spence (Newcastle): 'A clinical survey of 178 cases of pink disease.' These patients had all been personally observed in the Newcastle district during the past ten years. There was no distinct seasonal incidence. The mortality was 19 per cent. Investigation of the social and feeding history showed that the disease was prevalent in the well-cared-for and well-fed children. There was nothing to suggest a contagion, but three cases were mentioned in which pink disease affected successive children in the same family. Dr. Spence discussed the possibility of the disease being due to a positive toxic factor such as a mineral poison.

12. Dr. J. H. Ebbs (Birmingham), introduced by Prof. L. G. Parsons: 'Angiomatosis clinically resembling a lipoid granulomatosis.' A clinical and pathological report was given of a fourteen year old girl, showing clinical evidence of a possible 'osseous form of Gaucher's disease,' who at post-mortem examination, showed multiple cavernous haemangiomata of various sizes in the liver, spleen, retroperitoneal glands, thymus, mediastinum, lungs, pleura, kidneys and most of the bones in the body. The wide-spread involvement of the reticulo-endothelial system made the case a difficult one to classify, although histologically it appeared to be a case of multiple haemangiomata with histologically benign cells.

13. Dr. R. E. Smith (Rugby), introduced by Dr. A. G. Maitland Jones: 'The illness of infection of measles with special reference to the determination of the incubation period and the possibility of latent immunity.' The illness of infection of measles was first described by Goodall in 1925. In thirty-two years as medical superintendent of the London Fever Hospital, he saw seven or eight children who, after exposure to measles, developed symptoms highly suggestive of the disease, which disappeared in a day or two but were followed within the limits of the incubation period by a typical attack of measles. These cases appeared to be extreme examples of the condition, which usually manifests itself by a simple rise in temperature. In an epidemic among seventy-eight cases in 1934, five cases were observed. In 1936, routine temperatures were taken night and morning of thirty-seven non-immunes, and in this way six cases were discovered to have the illness of infection of measles, as demonstrated by a definite slight rise of temperature

after being in contact with measles. There were no other symptoms. Charts were shown of these cases, and also of two cases where the diagnosis was made but which did not subsequently develop measles. This phenomenon can be used to determine, with some degree of accuracy, the incubation period, which was found to be slightly longer than the one customarily given, being nine days in two cases, ten days in one, twelve days in one, thirteen days in four, and fifteen days in three. It is possible that the two cases which did not develop measles were examples of boys developing latent immunity which has lately been discussed by Stocks, who formulated a theory that for every child in a populous area who gets measles there are three latent cases. As in 1934 only fourteen out of ninety-two non-immunes escaped, and in 1936 only fourteen out of seventy-nine escaped, latent immunity must be extremely rare in public schools, and the difference between these figures and those of Stocks is probably due to the difference in density of population. Routine temperature taking was also of great use in diagnosing cases in the early stages, and the average length of the prodromal period was 2·2 days in forty-four cases compared with 1·1 in twenty-two cases which did not have their temperatures taken routinely, and the complication rate was less in the former than in the latter, although it was small in both.

14. Dr. T. Colver (London), introduced by Dr. D. Paterson: 'Chronic polyarthritis in children' (see p. 253).

15. Dr. J. D. Keith (Birmingham), introduced by Prof. K. D. Wilkinson: 'Conduction time and the first heart sound in acute rheumatism' (see p. 217).

TUMOURS OF THE SYMPATHETIC NERVOUS SYSTEM IN CHILDREN

A STUDY OF TWENTY-FIVE CASES

BY

RUBY O. STERN, M.D.,

Sebag-Montefiore Research Fellow, the Hospital for Sick Children, Great Ormond Street, London,

AND

G. H. NEWNS, M.D., M.R.C.P.,

Medical Registrar and Pathologist, the Hospital for Sick Children, Great Ormond Street, London.

Pepper[8], in 1901, in his paper entitled 'A study of malignant suprarenal tumours in children ' described six cases, all of which proved fatal during the first three months of life. In each there was a massive infiltration of the liver with metastases, the source of which was a growth in one of the suprarenal bodies. This combination of primary suprarenal tumour and secondary deposit in the liver has since come to be known as the Pepper syndrome. The first reference to bony metastases arising from a primary suprarenal tumour in a child was by Cohn[4] who reported a child who died at the age of nine months. The autopsy revealed a large tumour of the left suprarenal and metastases in the skull, ribs, liver, kidney and ovary. But it was not until 1907 that a clear account of this syndrome was given by Robert Hutchison[6] in his paper entitled ' On suprarenal sarcoma in children with metastases in the skull.' He regarded the tumours arising from the suprarenals as sarcomata. Four years later Frew[5] published a further series of twenty-nine cases, thirteen of which were patients in the Hospital for Sick Children, Great Ormond Street. Since then no further contribution to the literature on this subject has appeared from this hospital and as we have been able to verify pathologically twenty-five cases* the results seem worthy of record.

Although Wright[14] in 1910 pointed out that these tumours originated from nervous tissue and were not sarcomata, it is only during the last two decades that advances in technical methods have permitted their more exact

* Two cases were reported in the Proc. Roy. Soc. Med. (Children's Section), both by R. Lightwood, case 14 in 1932 and case 12 in 1933.

histological differentiation. Many cases of ' retroperitoneal sarcoma ' have thus been identified as tumours of the sympathetic nervous system. Several of the present series, for example, were originally given this diagnosis and only more detailed investigation of the material revealed their true nature.

As Scott, Oliver and Oliver[9] have recently reviewed the literature and have analyzed 158 cases it is proposed to refer only to some of the more important papers. The most exhaustive study made within the last few years in this country is that of Blacklock[3], who reported on eighteen tumours of the sympathetic system in children, twelve of which were examined pathologically. Sixteen were derived from the adrenal (nine from the right, seven from the left), one from the abdominal sympathetic ganglia, and one which arose in the left superior cervical ganglion. Blacklock maintained that pathologically there was no justification for the division of these tumours into the Pepper and Hutchison types, though as a clinical syndrome Hutchison's description should stand. The conclusions Blacklock came to regarding their pathology will be discussed later. In the series of seventeen cases reported by Askin and Geschickter[1], there were several in which secondary deposits were found in the bones as well as in the liver and other abdominal viscera. Such a combination of the Hutchison and Pepper syndromes was also found in the case reported by Sturtevant and Kelly[12]. Lewis and Geschickter[7] studied forty cases, of which eight were ganglio-neuromata. Half of these forty cases were in children under the age of three years. The Hutchison type occurred in the older children whose average age was six years.

General remarks

The series of twenty-five cases described in this paper covered a period of sixteen years (1921 to 1936 inclusive). Six of the autopsies were performed by one of us (G. H. N.). The rest were found in the post-mortem records often under other names. These twenty-five cases represented 0·9 per cent. of the total autopsies during this period.

Fifteen were males and ten females. The age incidence is given in table 1. From this it is seen that all but two of the girls were under the age of two whereas in the boys the highest incidence was in the third to fifth year. Four of the twenty-five patients were over the age of five at death; three of these were males.

Twenty-four of the tumours were abdominal. One arose from sympathetic tissue in the thorax. In view of its rarity a separate description of this tumour will be given.

An analysis of the early symptoms is as follows:—

Enlargement of the abdomen	9 cases.
Pain in the legs or limping	8 cases.
Pallor, wasting, listlessness (apart from other symptoms)	4 cases.
Swelling on the head	3 cases.

These were the symptoms that brought the child to hospital. In no case did proptosis of an eye occur early in the disease though it often appeared later. It is interesting to note that pain in the legs or limping

occurred almost as frequently as the enlargement of the abdomen from the rapidly growing intra-abdominal tumour. In the former group there was one patient who had a swelling in the upper part of the right thigh; in the others no clinical sign of a secondary deposit was present. Half of these eight patients were x-rayed and in these there were metastases in one or other of the long bones in the lower limbs. Tidswell and Sear[13] remarked on the frequency of this symptom of pain in the lower limbs, for it was present in every one of their eight cases.

Metastases are always more advanced in the lower than in the upper limbs. But the pain is probably caused not by deposits in the medulla of the bone but by elevation of the periosteum by tumour cells (see fig. 8). The same kind of sub-periosteal infiltration may occur in leukaemia. (A good description of the x-ray appearances and pathology was given by

TABLE I

AGE AND SEX INCIDENCE

	0–1 YR.	1–2 YR.	2–3 YR.	3–4 YR.	4–5 YR.	5–6 YR.	6–7 YR.	7–8 YR.
Males	3	1	2	3	3	1	1	1
Females	3	5	0	1	0	0	1	0
Total	6	6	2	4	3	1	2	1

Snelling, Brown and Erb[11].) The pain and tenderness in one of the present series of cases was so severe that a diagnosis of acute osteomyelitis was made.

In eight cases there was proptosis of one or both eyeballs at some time during the course of the disease and in eleven there were tumours on the head. This may be compared with the autopsy findings which showed that thirteen of the cases had bony metastases (only five of these were examples of the ' pure ' Hutchison syndrome).

In eleven patients the liver was enlarged, in some very greatly. In only three of these were there swellings on the head.

A moderate degree of fever was present in three-quarters of the patients. In a third of the total number it was periodic in type, the temperature being raised for a few days at a time. In one the periods resembled the Pel-Ebstein curve sometimes seen in lymphadenoma.

In twelve patients the blood was examined. A moderate anaemia was present in nine of these ; in the remaining three, the anaemia was severe, one having a red cell count of 1,400,000 per c.mm. and haemoglobin of 20 per cent. In seven of the anaemic patients the colour index was considerably below one. Of the remaining two, one had a colour index slightly above and the other slightly below unity. Three patients had a raised reticulocyte count—3 to 5 per cent., and one had many normoblasts and megaloblasts in the circulating blood. In none were there any significant changes in the

leucocytes nor were there any immature leucocytic cells in the peripheral blood.

Anaemia is commonly associated with malignant growths but in the neuroblastomata an important factor is the extensive haemorrhages into the tumours which so often occurs. A leuco-erythroblastic anaemia is occasionally met with. In these patients immature leucocytes and red cells appear in the peripheral blood. One of the patients in this series had a decided erythroblastosis. No bony changes were visible in the x-rays of this patient; nor were any to be seen in the case shown by Hart* at the Royal Society of Medicine, Children's Section in May, 1937, although there was a severe anaemia with large numbers of immature white and red cells in the blood. The cause of this leuco-erythroblatosis could not be a massive infiltration of the bone-marrow with secondary deposits as it is in carcinomatosis of bones. It is probably caused by a generalized cellular infiltration of the bone-marrow with malignant cells. If this were so x-ray changes would not be expected. The normal bone-marrow cells would, however, be stimulated excessively and many immature cells would appear in the circulating blood.

When metastases are present in the skull the x-ray shows diffuse mottling and separation of the sutures. These changes are well seen in fig. 10. The same mottled appearance also occurs in the long bones. In these there may be a characteristic elevation of the periosteum resembling what is sometimes seen in leukaemia (fig. 9). It is due to subperiosteal infiltration with tumour cells and is probably the cause of the limb pains which occur in both these diseases. Occasionally in the skull and long bones a striking spiculation may be observed (fig. 9). Less than a third of the present patients were x-rayed and in only the more recent ones were the long bones included. The skull was normal in most cases x-rayed but two showed well-marked mottling. In four there were secondary deposits in the bones of the lower limbs.

The prognosis is hopeless, for by the time the patient comes under observation the tumour is inoperable, either by reason of its great size or because of the presence of secondary deposits. The course of the disease is a relatively short one. Only two patients survived for more than six months from the onset of the symptoms, ten lived from three to six months and twelve died in less than three months from the first symptom. Askin and Geschickter[1] found that the average duration of symptoms before observation in their series was six months, though in half of the patients it was one month or less.

Many cases of neuroblastoma are only recognized at autopsy and even then their true nature may be missed. In the present series they have been found under other diagnoses such as retroperitoneal sarcoma, Wilms' tumour and sarcoma of the liver. The incidence of neuroblastoma and Wilms' tumour is about the same. The former, however,

* Reported in the Lancet, 1937, i, 1458.

remains localized for a long time. Metastases appear late and spare the bones. When, therefore, an abdominal tumour is found in early life in association with a tumour on the head or secondary deposits in the long bones it is almost certainly a neuroblastoma. In young babies, the disease often takes the form of an extreme enlargement of the liver. Such cases, frequently diagnosed as sarcoma of the liver, are in reality sympathetic suprarenal tumours of the Pepper type, the primary growth being small and the liver massively infiltrated with metastases (see fig. 4).

Morbid anatomy

It has already been mentioned that some of these cases had been misdiagnosed as retroperitoneal sarcomata, the reason being that the tumour occupied the whole of the posterior part of the abdomen, and did not seem to be arising from either suprarenal. An analysis of the cases showed that this variety is by no means uncommon. In four cases, despite the presence of an enormous mass, neither suprarenal was involved macroscopically or microscopically in the growth. We assumed that in these cases the origin of the tumour was not from the suprarenal but from the abdominal sympathetic chain. In others, one or other suprarenal was definitely included in the tumour mass the origin of which was probably from the sympathetic tissue of that organ (fig. 1).

It is customary to classify these tumours into the Hutchison and Pepper types, but Scott et al.[9], Blacklock[3], Askin and Geschickter[1] and others have pointed out that in many cases no such clear distinction can be drawn. This is borne out by the present figures. While five of the cases presented solely the features which Hutchison described, and five those of the Pepper syndrome, in no less than nine there were both bony and visceral metastases. In four cases only the kidney and the adjacent lymph glands were involved, and in one of the two ganglioneuromata there were no metastases.

Lewis and Geschickter[7] stated that the Hutchison syndrome was commoner in older children, the average age in their series being over six years. It was found, however, in the present series that there was little difference in age distribution between the Hutchison and Pepper types, the average age for the former being three-and-a-half years and for the latter slightly under two-and-a-half years. Whilst, generally speaking, bony metastases occurred in older children yet they were found frequently in the very young child. The average age for the ' mixed ' type was two years and eight months.

Scott et al. in their analysis of 158 cases did not discover any predilection of the growth for one side, nor could they demonstrate any relationship between the side of origin and the site of metastases. This series confirms these observations. The tumours arose with equal frequency from the two sides, eight arising from the right suprarenal and eight from the left. In three, both suprarenals were involved; in one the state of the suprarenals was not mentioned.

FIG. 1.

CASE 2.—Large retroperitoneal mass. The right kidney is almost completely replaced by growth. A few small secondary deposits are present in the liver.

FIG. 2.

CASE 7.—The tumour shows cystic degeneration. The kidney is pressed on but not invaded.

FIG. 3.

CASE 4.—Anterior half of tumour showing primary growth in right suprarenal. Left suprarenal normal. Note the large mass between the kidneys and the hydronephrosis of the right kidney due to obstruction of the ureter.

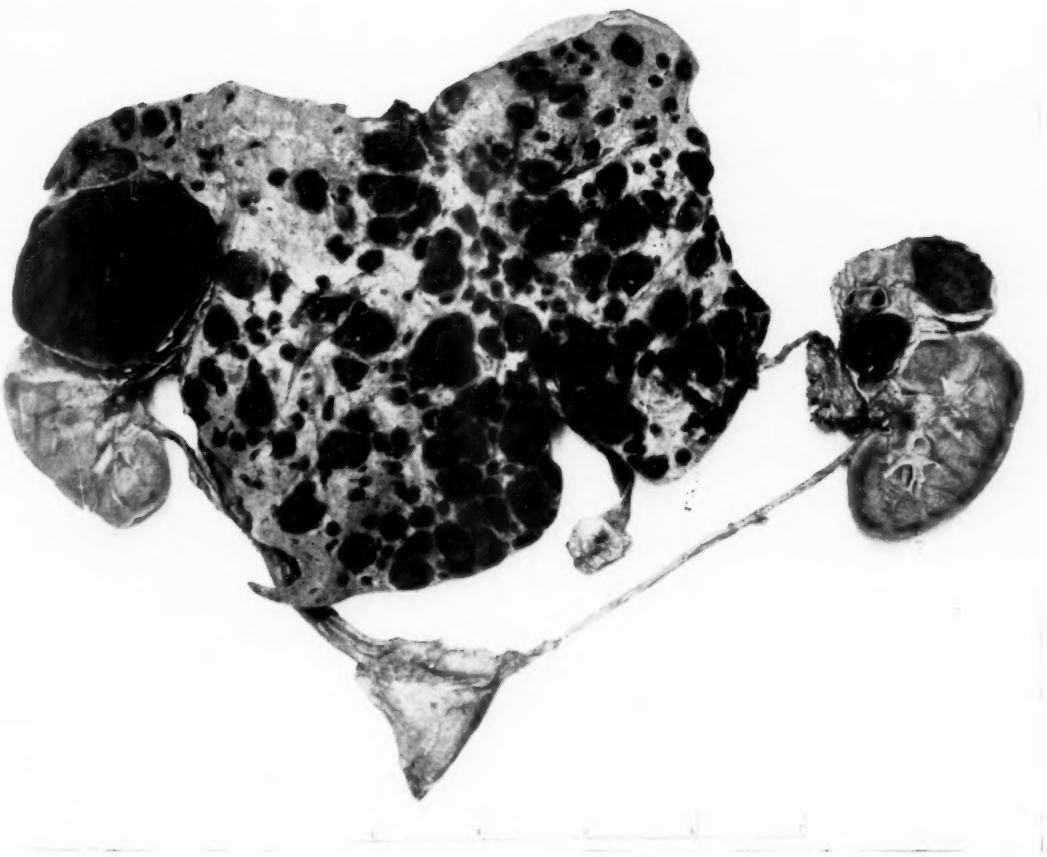

FIG. 4.

CASE 10.—Large growth in right suprarenal, and a smaller one in the left. The liver is studded with metastases (Pepper syndrome).

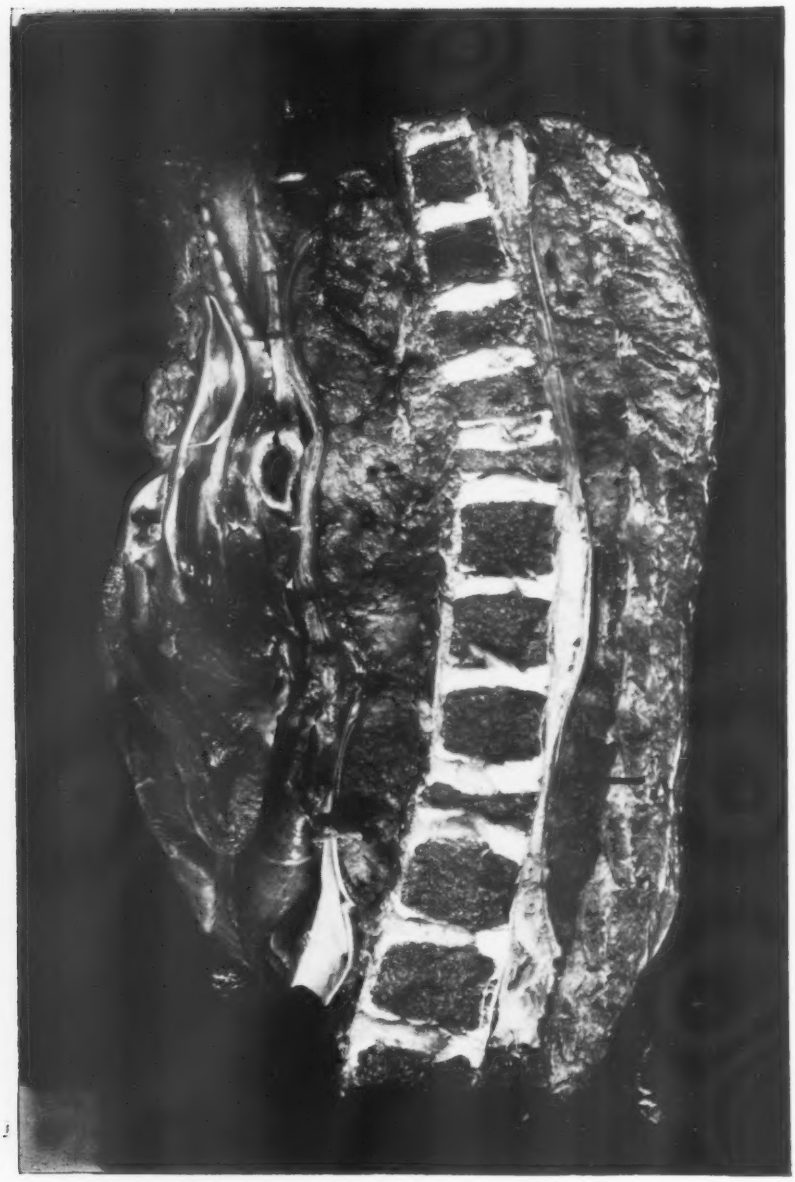

FIG. 5.

CASE 15.—Thoracic tumour. The arrow points to the place where the cord is compressed by the growth.

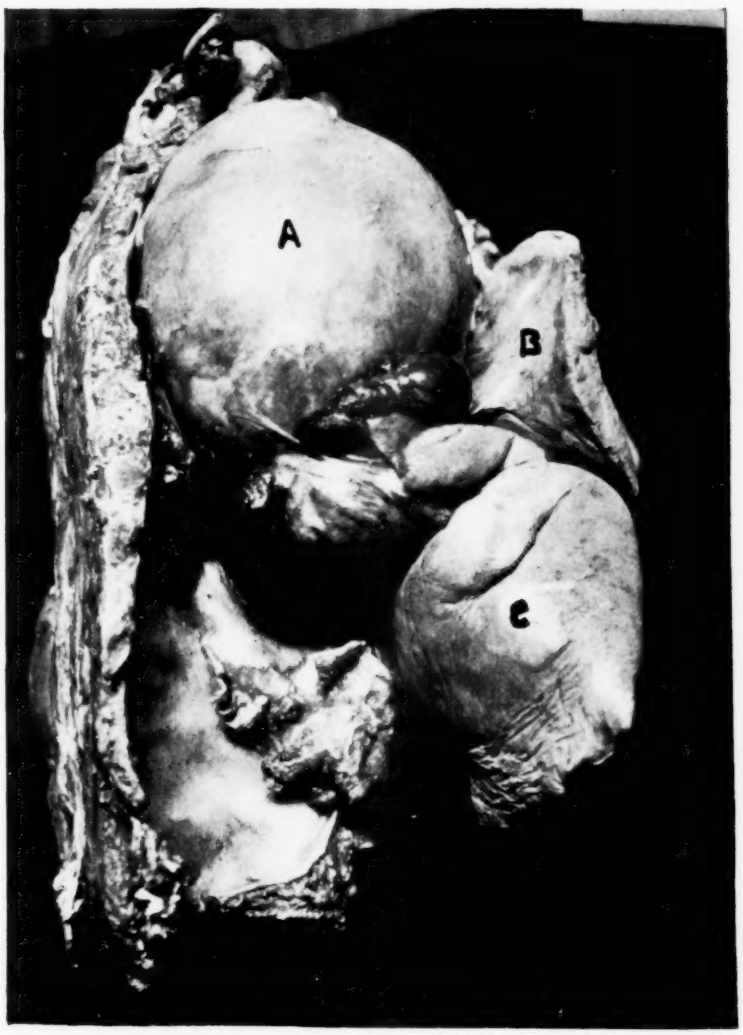

FIG. 6.

CASE 15.—Thoracic tumour. A. The main part of the tumour. B. The compressed right upper lobe. C. The right lower lobe which was invaded by growth.

FIG. 7.

CASE 5.—Large secondary deposit in the femur. The x-ray of the same case at an earlier stage is shown in fig. 9.

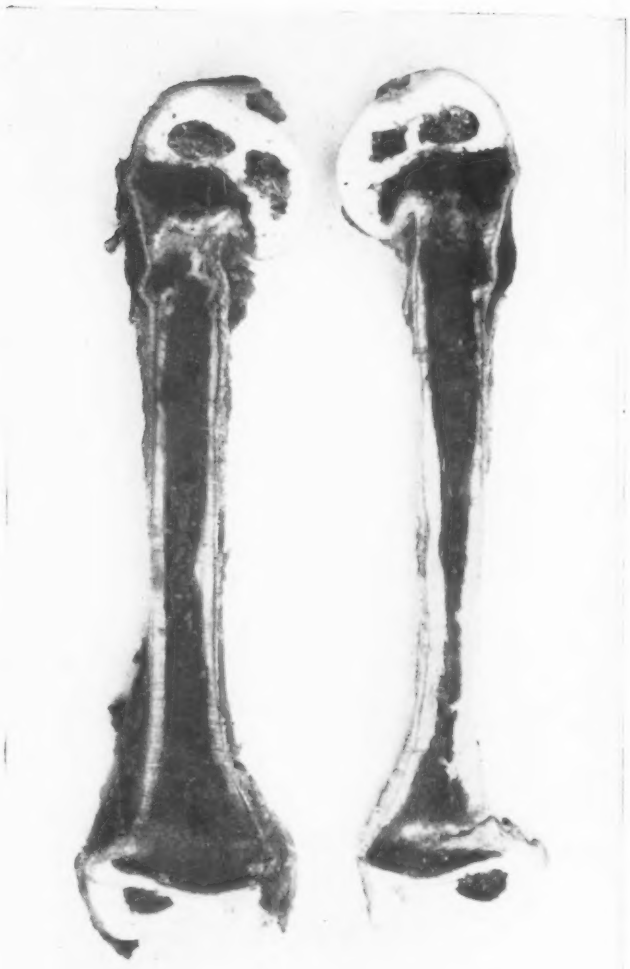

FIG. 8.

CASE 7.—Humerus showing raising of the periosteum. Deposits are also present in the bone marrow.

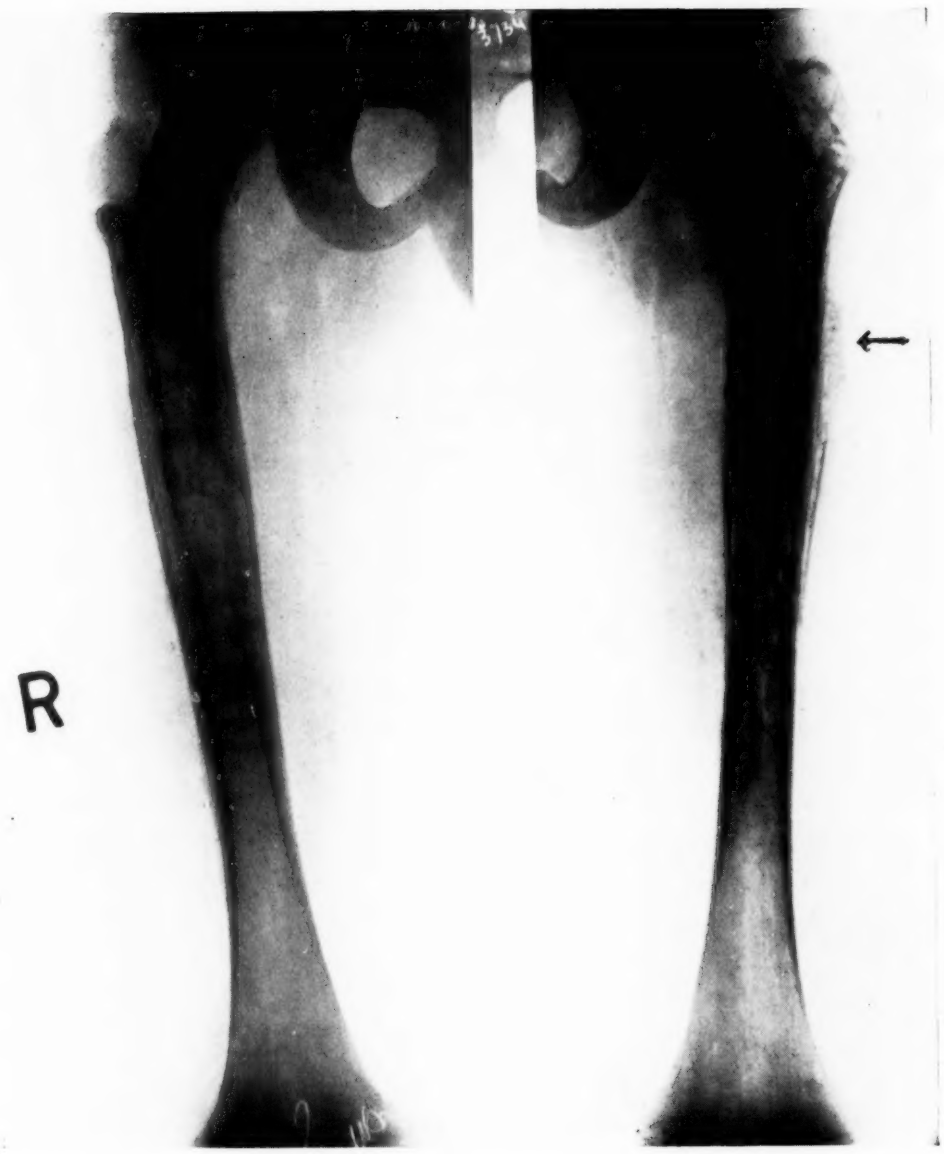

FIG. 9.

CASE 5.—Elevation of the periosteum of both femora. Spiculation is indicated by the arrow.

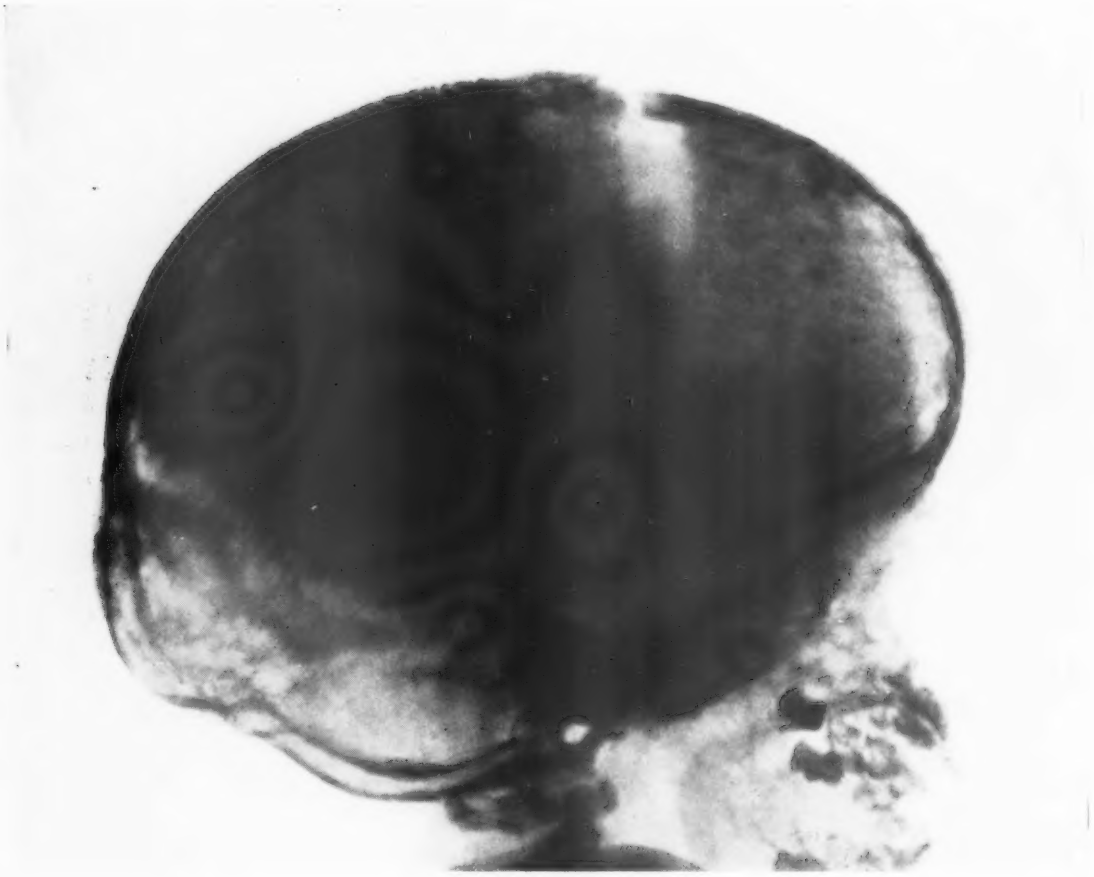

FIG. 10.

CASE 14.—The x-ray shows diffuse mottling of the skull and separation of the sutures.

Distribution of visceral metastases

Besides the metastases which were present in the liver in thirteen cases, macroscopic deposits were found in many other viscera. In five cases intrapulmonary metastases were seen, but the pleura was not involved. This contrasts with Blacklock's findings, for in two out of four of his cases with thoracic deposits, there was a malignant pleurisy with a haemorrhagic effusion. Blacklock also found a surprisingly large number of metastases in the pancreas—in seven out of eleven cases. We were able to trace only two such metastases in the present series of twenty-five. It is generally recognized that the kidney is pressed upon rather than invaded and we were surprised to find that in a third of the cases a spread to the kidney had occurred (see fig. 1). Rare sites for metastases were the intestine (two cases—one in the caecum and the other in the colon) and the ovary (one case only). There was one example of a metastasis in the brain. This was

in the parietal lobe adjacent to a large haemorrhagic deposit in the dura (case 5).

Histology

Although the characteristic structure of tumours of the sympathetic system arising from the adrenal medulla had been recognized as long ago as 1864 by Virchow, it was not until 1910 that Wright[14], by comparison with the adrenals of embryos, was able to show the resemblance between the arrangement of the tumour cells and that of foetal adrenal medulla and sympathetic ganglia. He was therefore the pioneer of a classification for these tumours based on their histology. Since then, a number of classifications, with many sub-divisions, most of them complicated and unwieldy, have been devised. These are not quoted as they are given in detail in the historical review of Scott et al[9]. Whilst it is desirable that a terminology should be used by which tumours consisting of a primitive type of cell can be distinguished from those in which mature cell types predominate, pure cell types occur only rarely in these tumours and the cellular form may vary greatly from one part of the tumour to the other. Consequently it is strongly felt that unwieldy and complicated classifications should be abandoned in favour of a simplified one which embraces the main cellular types encountered. A brief description of the essential features of the sympathetic nervous system is necessary in order to present the simple classification which Bielschowsky[2] evolved and which we have adopted here.

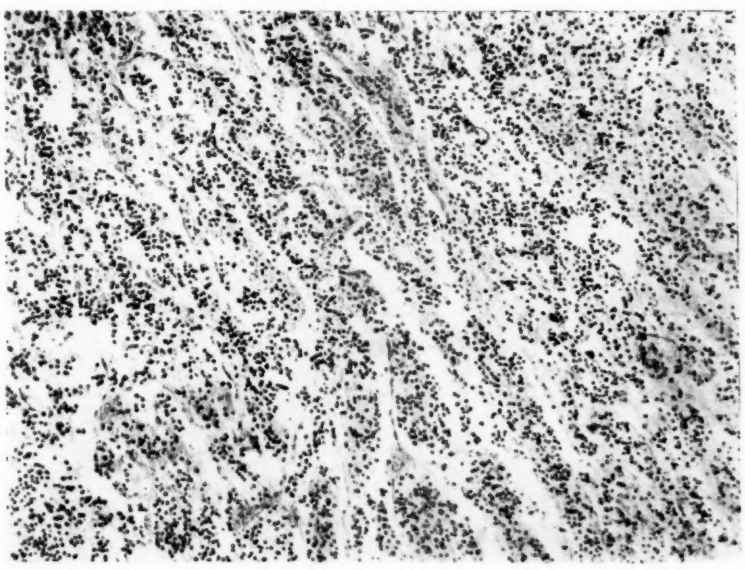

FIG. 11.

General view of section from case 20 to show cells arranged in columns separated by strands of fibrous tissue.
Stain: haematoxylin and Van Gieson. × 100.

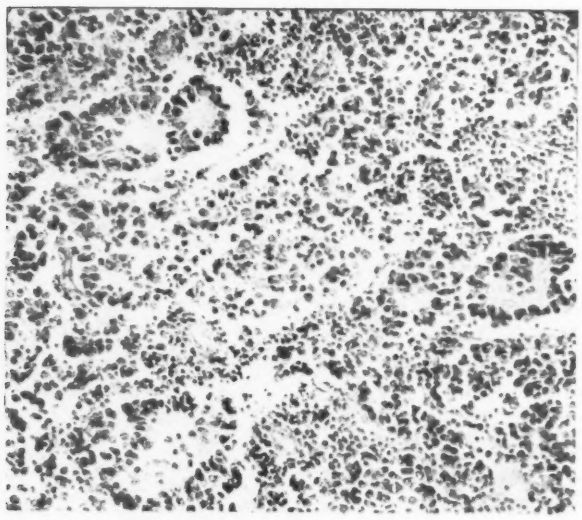

FIG. 12.

Low-power photograph of section from case 22. Four pseudo-rosettes are seen, two of them adjacent to each other. There is much variation in the size and shape of the cells.
Stain: haematoxylin and eosin. × 100.

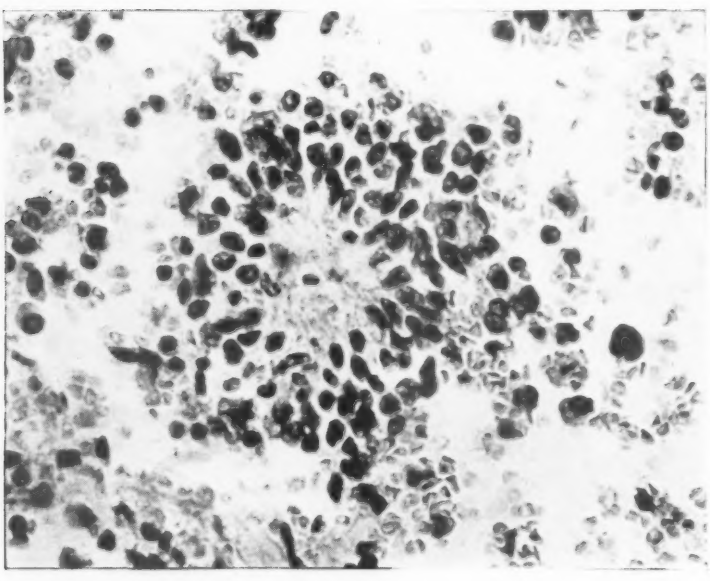

FIG. 13.

High-power view of pseudo-rosette (case 23). The fibrillar material in the centre of the rosette is formed by processes arising from the cytoplasm of the innermost layer of cells.
Stain: haematoxylin and eosin. × 400.

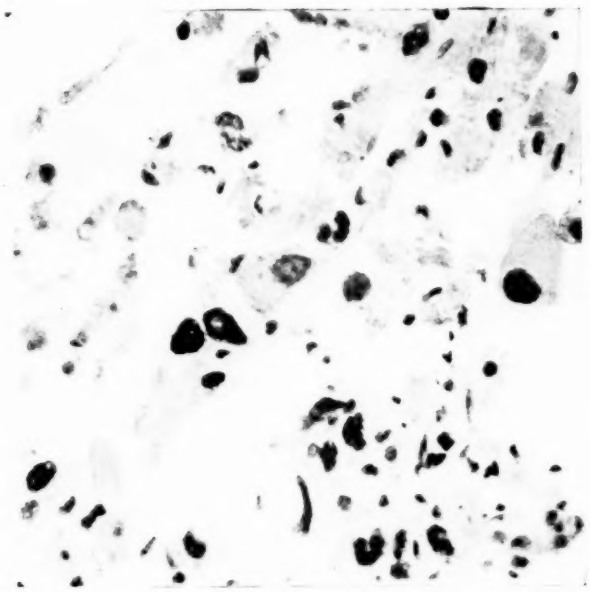

FIG. 14.

Section of ganglioneuroma (case 16). Three large cells resembling sympathetic nerve cells are present in the field. Smaller, less differentiated cells are also to be seen.
Stain: haematoxylin and eosin. × 400.

The parent cell of the sympathetic nervous system is the sympathogonia, a small rounded cell resembling a lymphocyte, with a densely staining nucleus and only a small ring of cytoplasm in which no processes can be identified. This cell is multipotential and gives rise to both ganglion cells and to the chromaffin cells. The next stage in development is the sympathoblast, a larger, more polygonal shaped cell possessing a considerable amount of cytoplasm in which fine fibrils may be seen. The cytoplasm is prolonged at one end of the cell body into a short process. The nucleus is large and the chromatin is finely divided, giving a vesicular appearance to the nucleus. The adult mutipolar ganglion cell with intracellular fibrils and Nissl granules in the cytoplasm represents the final stage in development. Corresponding approximately to these three stages in development, though often no arbitrary line can be drawn, there may occur three varieties of tumour of the sympathetic system and on this basis the simplest classification would be:—

1. Tumours consisting of completely undifferentiated cells. (Sympathogoniomata.)

2. Tumours in which the predominating cell resembles a sympathoblast. (Sympathoblastoma.)

(This tumour is extremely rare. Bielschowsky[2] was able to find only one example in the literature.)

3. Tumours which contain mature ganglion cells. (Ganglioneuromata.)

It is common to find cells resembling both sympathogoniomas and sympathoblasts in one tumour and it is this intermediate group which has caused such confusion in nomenclature. No name for it has received general acceptance. According to the above classification the accurate term for it would be ' sympathogonioblastoma ' and this is the term which we propose to adopt.

In the present series there were six examples of sympathogoniomata, sixteen of the ' mixed ' type of tumour, the sympathogonioblastoma, none of a true sympathoblastoma, and two ganglioneuromata. In one case no sections were available for study. Two of the sympathogoniomata occurred in the youngest children in the series, aged three and five months respectively. This was not surprising as it is generally accepted that the most primitive cellular types occur more frequently in younger children. Nevertheless, one example of this type of tumour was in one of the oldest children in the series, aged three-and-a-half years (case 14).

Although the individual cells in the sympathogoniomata all showed the same characteristics, namely, densely staining nuclei, little cytoplasm and many mitotic figures, their arrangement varied considerably. In some cases the cells were closely packed together in dense masses with no connective tissue separating them, giving a picture resembling a small round-celled sarcoma. In others there was a definite alveolar arrangement, the cells being grouped into alveoli, separated from each other by strands of firm fibrous tissue (fig. 11). In none of the sympathogoniomata were any pseudo-rosettes observed. These were found only in the slightly more differentiated sympathogonioblastomata of which there were sixteen examples. The microscopical picture of these tumours varied greatly. Haemorrhage was a feature of nearly every case and in some there was difficulty in making out the histological details. When autopsy material was available, as in the more recent cases, fresh sections were made from less haemorrhagic and degenerated parts of the tumours. In some sections in this group the cells contained much cytoplasm and were arranged in alveolar formation with strands of fibrous tissue separating the alveoli. In others, in which the cellular types were intimately mixed the cells were loosely packed, showed no orderly arrangement, but had strands of connective tissue between irregular masses of cells. We were able to demonstrate rosettes in ten cases, though usually many sections had to be examined before a few rosettes were discovered. We were unable to demonstrate fibrils in the centre of the rosettes by Gros's silver method, but they were easily identifiable by van Gieson's counterstain, with which they stained a buff colour, and by Mallory's phosphotungistic acid haematoxylin (fig. 13). A perivascular arrangement of the cells was not uncommon, giving rise to another variety of ' pseudo-rosette.' The amount of fibrous stroma was variable, but as might have been expected in a tumour with more differentiated cells, it was greater than in the sympathogoniomata. It was

surprising to find that the two cases of ganglioneuromata occurred in young children. These patients were aged fourteen months and nineteen months respectively (cases 15 and 20). Whilst many mature nerve cells were present, sympathoblasts were also seen. A section from case 15 is seen in fig. 14.

Description of thoracic growth (fig. 5 and 6)

The patient was a girl age seven years who had a flaccid paralysis of both legs and loss of sensation up to the level of the sixth dorsal segment. The shadow of the tumour could be seen in an x-ray of the chest. At autopsy a large growth was found occupying the posterior mediastinum. It could not be separated from the bodies of the vertebrae or the posterior parts of the ribs. The aorta was stretched out over the front of the mass and the upper lobe of the right lung was displaced forwards. The lower lobe was invaded by growth. Large secondaries were present in both pleurae. The tumour had infiltrated the epidural space and compressed the spinal cord. The liver and both suprarenals were normal. Histologically the tumour was a sympathogonioblastoma and it must have arisen from the thoracic sympathetic chain.

Discussion

Although this study adds nothing original to the well-defined clinical description of these sympathetic tumours, certain features not hitherto generally recognized attracted special attention and deserve mention. The first is the frequency with which pain in the limbs occurs as an early or even as the only presenting symptom. In no less than eight of the patients, one-third of the total number, the initial complaint was of pain in the legs or limping. Only four of these eight patients had x-rays taken of the long bones, but in these, metastases were visible. A tumour of the sympathetic system must therefore be considered when a child complains of persistent pain in the legs for which there is no obvious cause. Attacks of periodic fever were present in one-third of the cases. Whilst slight fever is often associated with the occurrence of malignant growths, particularly in the thorax, the periodicity of these attacks was striking, and in one abdominal case the fever resembled the true Pel-Ebstein type. The age incidence was different from that recorded in other series. Scott et al. found that in thirty-eight cases of the Hutchison type the tumour occurred at an average age of 8·5 years when originating in the left adrenal and at 3·5 years when originating in the right, whilst the Pepper type (thirty cases) occurred at an average age of 2·5 months when primary in the right adrenal, 15·5 months when in the left. In the present series the average age for the Hutchison type was 3·5 years, for the Pepper type 2·3 years. Nine tumours of the ' mixed ' type had an average age incidence of 2·7 years. In view of the high proportion of cases in which there were both bony and visceral metastases and the slight difference in age incidence between the ' Hutchison ' and ' Pepper ' types, it is considered, as Blacklock has already intimated, that the only justification

for separating these two types is clinical convenience; there is no etiological or pathological distinction. Bony metastases may occur at an early age (case 4, one year old) and older children may have only visceral deposits (cases 19 and 6, 5·8 and 3·5 years respectively).

Pathologically one of the chief points of interest was the incidence of the two cases of ganglioneuroma in children aged fourteen months (case 15) and nineteen months (case 20). Certainly in case 20 the tumour was more malignant than is usual in a simple ganglioneuroma as it had invaded the kidney. No other metastases were present, and microscopically the tumour contained many well-formed ganglion cells. These tumours are rare in children, and particularly in infants. Scott et al. could trace only four arising in the adrenal medulla in children; in two of these the ages were between four and five years (in the other two the age was not stated). Two out of the eight cases of ganglioneuromata recorded by Lewis and Geschickter occurred in children aged four and ten years respectively, but Blacklock's patient was an infant of one year and ten months.

An unusual feature of the morbid anatomy was the high incidence of metastases in the lung. These were present in five cases and formed obvious intrapulmonary masses, the pleura being unaffected. Metastases in the brain are rare enough to be noteworthy. In case 5 there was a definite tumour mass present in the parietal lobe underlying the bone which was the site of a large deposit. The tumour had extended through both tables of the bone and had penetrated through the dura, invading the brain by direct extension.

As regards the histological structure of the tumours, we reached the same conclusion as other observers, namely, that these sympathetic growths nearly always contain cells in different stages of development; in some parts of a very immature type of cell and in others a more differentiated type of cell predominates. Even in the two examples of a fully differentiated tumour (ganglioneuroma) encountered the tumour did not consist entirely of ganglion cells. In view of this fact it seems purposeless to elaborate a complex and confusing terminology based on slight differences in the morphology of the component cells. In spite of the advances which have been made in the identification of sympathetic cells in various stages of development, for practical purposes it is sufficient to differentiate the main types corresponding to the main developmental cells. We therefore consider it wise to adopt the simple terminology of Bielschowsky[2] which has been used in the description of the histology of the present cases. As a general term for the group of sympathetic tumours as a whole, the name 'sympathoblastomata' is suggested in preference to the commonly employed 'neuroblastomata.' The latter term affords no indication of the sympathetic origin of the tumours besides being the name given to a tumour occurring in the central nervous system,

TABLE 2

No.	Sex	Age in years	Adrenal involved	Kidney involved	Liver metastasis	Lung metastasis	Bone metastasis	Other metastases	Histological classification
1	M.	$2\frac{4}{12}$	Left	Yes	No	No	R. orbit and 9th r. rib	Head of pancreas	Sympathogonioblastoma
2	F.	2	R. incorporated with tumour	Yes	Yes	No. Primary tub. focus in l. lower lobe	Both tables of r. frontal and parietal bones 8th r. rib	—	Sympathogonioblastoma
3	F.	$1\frac{11}{12}$	L. incorporated with tumour	No; L. kidney completely surrounded but not invaded	No	No	Both tables of r. frontal	—	Sympathogonioma
4	F.	1	Right	Yes	No	No	R. frontal and parietal bones; base of skull, spinal column and ribs	Submucous and muscular coats of caecum	Sympathogonioblastoma
5	M.	$6\frac{1}{2}$	Left	No	No	No	Frontal bones: femur, humerus, ribs	Small degenerating deposit in parietal lobe and dura	Sympathogonioblastoma
6	F.	$3\frac{1}{2}$	Right	No	Yes	Yes	No	—	Sympathogonioblastoma
7	M.	5	Right	No	Yes	No	Humerus; ribs, tibia	—	No sections available
8	M.	$1\frac{9}{12}$	Right	Yes	No	No	No	—	Sympathogonioblastoma
9	M.	$1\frac{3}{12}$	Both	No	Yes	Yes	Many cranial bones	Dura mater	Sympathogonioma
10	F.	$1\frac{5}{12}$	Both	No	Yes	No	No	—	Sympathogonioma
11	M.	$3\frac{4}{12}$	Neither	Yes	Yes	Not mentioned	Cranial bones	Dura mater	Sympathogonioblastoma
12	M.	$1\frac{6}{12}$	Not mentioned	No	Yes	Yes	No	—	Sympathogonioma

TABLE 2—*continued*

No.	Sex	Age in years	Adrenal involved	Kidney involved	Liver metastasis	Lung metastasis	Bone metastasis	Other metastases	Histological classification
13	M.	$2\frac{6}{12}$	Left	Yes; microscopically only	No	No	No	—	Sympathogonioma
14	M.	$3\frac{1}{2}$	Neither	No	No	No	Cranial bones, ribs, long bones	—	Sympathogonioma
15	F.	7	Neither	No	No	Yes Thoracic tumour	No	—	Sympathogonioblastoma
16	F.	$1\frac{4}{12}$	Right	No	No	No	No	—	Ganglioneuroma
17	M.	$3\frac{10}{12}$	Left	Yes	Yes	Yes—extensive	Skull, ribs	—	Sympathogonioblastoma
18	M.	$4\frac{1}{2}$	Left	No	No	No	Skull	—	Sympathogonioblastoma
19	M.	$\frac{11}{12}$	Right	No	Yes	Yes	No	—	Sympathogonioblastoma
20	M.	$5\frac{10}{12}$	Neither	No	Yes	No	No	—	Sympathogonioblastoma
21	F.	$1\frac{9}{12}$	Right	Yes	No	No	No	—	Ganglioneuroma
22	F.	$\frac{11}{12}$	Left	No	Yes	No	Skull	Dura mater	Sympathogonioblastoma
23	F.	2	Neither	Yes	No	No	Ribs, skull	Intestine (duodenum and colon), ovaries	Sympathogonioblastoma
24	M.	8	Both	Yes	No	No	No	Many mesenteric and preaortic glands	Sympathogonioblastoma
25	M.	$4\frac{1}{2}$	Left	No	Yes	No	Skull; ribs	Head of pancreas	Sympathogonioblastoma

Summary

1. A study has been made of twenty-five cases of sympathetic nerve tumours. Twenty-four were in the abdomen. Because of its rarity, the thoracic case is described in greater detail.

2. Two-thirds were in males and one-third in females. The average age of the Hutchison group was three-and-a-half years, of the Pepper group two-and-a-half years, and of the children with bony and visceral metastases two years and eight months. The average age of the patients with the Hutchison syndrome was lower and of those with the Pepper syndrome higher than that of other series described in the literature.

3. In many cases the tumours formed large retroperitoneal masses. In a small proportion of these the suprarenals were normal and the tumour must have arisen from the abdominal sympathetic chain.

4. The tumours arose from either side with equal frequency. There was no relation between the side of origin and the situation of the metastases.

5. Metastases were found in the kidneys, lung, pancreas, intestine, ovary and brain, as well as in the liver and bones.

6. The commonest early symptoms were pain in the lower limbs with limping and abdominal swelling. Periodic fever was a common feature. Hypochromic anaemia, partly due to large haemorrhages into the tumour, was present in half the cases.

7. The presence of metastases in bones distinguishes the tumour from Wilms embryoma, the other common malignant growth of early childhood.

8. The histological structure of the tumours is described and a simplified classification proposed. The name sympathoblastoma is suggested as a general term for this class of tumours.

We wish to express our thanks to the Honorary Staff at the Hospital for Sick Children for allowing the use of the case records; to Dr. D. N. Nabarro, Director of the Pathological Department for his unfailing interest; and to Mr. Deryck Martin who has devoted much time to preparing the photographs. The photomicrographs were taken with an apparatus the cost of which was partly defrayed by a grant from the Thomas Smythe Hughes fund.

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CEREBRAL TUMOURS IN CHILDREN

A PATHOLOGICAL REPORT

BY

RUBY O. STERN, M.D.

(Sebag-Montefiore Research Fellow at the Hospital for Sick Children, Great Ormond Street.)

Rapid advances in neurosurgery and recently acquired knowledge of the growth and spread of cerebral tumours based on their microscopical differentiation have given an impetus to the study of these tumours from divers aspects. The dictum that cerebral tumours are rare in children but are almost invariably malignant and inoperable has long been accepted. For this reason perhaps there have been few reports of late years from children's hospitals on the pathology of these tumours. With one or two exceptions the material recently presented on this subject has been derived from special neurological hospitals and clinics. New facts have emerged from some of these reports regarding the incidence and structure of cerebral tumours in children and a more hopeful note on prognosis has been sounded. It was therefore felt that an examination of the cerebral tumours at a large general hospital for children and particularly a study of their microscopy based on a modern classification might yield certain information. The results of this examination are presented in this paper.

General considerations

The investigation covered a period of fifteen years, from 1921 to 1935. This period was taken in order to obtain as large a series of tumours as possible. Sections from specimens prior to 1921 were not available. Particulars of all cases diagnosed clinically as ' cerebral tumour ' were obtained and whenever possible the topographical distribution and histological nature of the tumours were ascertained of those patients who died and on whom an autopsy was performed. If autopsy material was available frozen sections and blocks embedded in celloidin were cut. If only paraffin blocks were to be found then fresh sections were stained by a variety of methods. The stains used for the preparation of these new sections were iron haematoxylin with van Gieson's counterstain, Mallory's phosphotungstic acid haematoxylin and, in some cases, Anderson's victoria blue stain and Hortega's silver carbonate stains. In some of the earlier cases a diagnosis had to be made by examination of a section stained by the routine method of haematoxylin and eosin. In a few instances this was

impossible. Sections were missing from a few cases and in these no diagnosis could be made as it was idle to speculate on the nature of the tumour from the description of its macroscopical appearance and futile to attempt to elucidate the previous microscopical diagnosis of ' sarcoma ' or ' glio-sarcoma.'

It is necessary to emphasize that only cases diagnosed clinically as ' cerebral tumour ' are considered here. During a perusal of the post-mortem records no cerebral neoplasms were encountered which had not previously been diagnosed, but a number of small tuberculomata were traced the presence of which had not given rise to symptoms of tumour. In these cases the cause of death was tuberculous meningitis. The question arose if these cases, in most of which the tuberculomata were only just visible macroscopically, were to be included in a report on ' cerebral tumours.' In other recent studies of cerebral tumours in children this has not been done and for this reason it was decided not to include such cases in this report. A note on these tuberculomata will appear elsewhere. Here are included only those tuberculomata in which a diagnosis of cerebral tumour was made —six in all—and in three of these a decompression operation was performed.

In the older literature on cerebral tumours tuberculomata were considered to be the most common tumour in childhood. Starr[16], for example, found over 50 per cent. of his 300 cases of cerebral tumour in children were tuberculomata. It is not clear, however, if these all represented masses giving rise to the symptoms and signs of cerebral tumour or if they included the small tuberculomata discovered accidentally at post-mortem examination of cases of tuberculous meningitis. Garland and Armitage[11] in their survey of intracranial tuberculomata (which included all tiny multiple tuberculomata found in the brain in tuberculous meningitis), concluded that tuberculomata constituted 60 per cent. of all intracranial tumours in children. This is only true if tiny masses present in the brain in certain cases of tuberculous meningitis are included in a classification of cerebral tumours. Van Wagenen[17] stated that in 140 cases of cerebral tumour in patients under nineteen years of age only five (3·5 per cent.) had tuberculomata, whilst in ninety-eight cases of tuberculous meningitis macroscopical tuberculomata were present in nine (9·1 per cent.). Similarly Cushing[8] in his series of 154 cases of cerebral tumour in children under fifteen years of age could find tuberculomata only in six (3·9 per cent.).

The frequency of intracerebral tuberculomata excluding those found accidentally in cases of tuberculous meningitis would therefore seem to be low. The figures in the present series, based on the same distinction, also reflect this low incidence.

The incidence of cerebral tumours in children

One hundred and two cases of cerebral tumour were diagnosed during the period under review. Of thirty-seven children in whom the diagnosis was made and who left the hospital, six were transferred to other hospitals (two subsequently had a tumour successfully removed at the London Hospital), three were reported as showing ' slight improvement ' (two after a decompression); two were taken home by their parents; twenty were

discharged ' in statu quo '; the condition of three was ' worse '; and in three cases no note was recorded on discharge. There were sixty-five deaths and autopsies were performed on sixty-two cases. The total number of post-mortem examinations performed during the same period was 2,808, so that cerebral tumours accounted for 2·2 per cent. of all autopsies. It would be valueless to give the apparent clinical incidence of these tumours calculated from the figures for total admissions to the hospital during the fifteen years as a large number of children were admitted for one day only for recovery from tonsillectomies or for dental treatment and therefore figures so calculated would convey a false impression of the incidence of cerebral tumour in relation to other diseases of childhood.

The autopsy figures were high compared with those of Wollstein and Barlett[18] who were able to collect only nine cases of cerebral tumour in 4,563 autopsies (0·2 per cent.), at the Babies' Hospital, New York. The difference in these figures cannot be attributed to the fact which some observers have stated, that more cerebral tumours occur in older children. Critchley[7], for example, in reporting 125 cases in children under the age of fourteen out of 1,028 cases diagnosed as cerebral tumour at the National Hospital, Queen Square, found that only three occurred under three years of age, whilst Russell and Ellis[13] in fifty-three verified cases of gliomata in children met with only twelve in the first five years of life.

In the present series (taking the 102 cases diagnosed), fifty-four—that is over half—occurred in children under the age of five years, and forty-eight between the ages of five and twelve years. Of the cases which came to autopsy there were thirty-five in the first five years of life and twenty-seven between five and twelve years. The absolute age incidence is given in table 1. Certain points in this table should be mentioned. The first is the number of tumours which occurred in the first two years of life, fourteen, all of which came to autopsy and constituted over a quarter of those thus verified. Their pathological nature will be discussed later, but it may be remarked here that only two of the tuberculomata fell within this age

TABLE 1

AGE INCIDENCE. (ALL TUMOURS).

	0–1 YR.	1–2 YR.	2–3 YR.	3–4 YR.	4–5 YR.	5–6 YR.	6–7 YR.	7–8 YR.	8–9 YR.	9–10 YR.	10–11 YR.	11–12 YR.
All cerebral tumours diagnosed (102)	6	8	14	16	10	7	14	5	5	6	6	5
Tumours verified post mortem (62)	6	8	8	8	5	6	10	2	3	2	2	2
Unverified (40)	0	0	6	8	5	1	4	3	2	4	4	3

period. Another point which emerged from this table of age incidence was the early age at which most cerebral tumours occurred. Thirty out of the 102 were found during the age period two to four years, though of these fourteen were in the unverified clinical group. Taking the verified group separately, this age period shared the highest incidence with that of five to seven years (sixteen cases for each period). It is noteworthy that the incidence for each of the five years from seven to twelve was practically the same.

There was no appreciable difference in the sex incidence. Of the total number fifty-five were boys and forty-seven girls. Autopsies were made on thirty-seven boys and twenty-five girls, this proportion of boys to girls being slightly less than the proportion of boys to girls for all autopsies over the same period. (Males 57·84 per cent.; females 42·16 per cent., 1·37 to 1). Although there was no difference between the sexes in regard to the incidence of cerebral tumours in general, one particular type of tumour, the medulloblastoma, occurred nearly three times more often in boys than in girls. Cushing[8] and Armour[1] have previously remarked that this tumour appears to preponderate in boys; they gave the ratio of 3 to 1.

Topographical distribution

Every writer on the subject has emphasized the essential difference in localization between cerebral tumours in children and in adults. In children the majority of tumours lie in the subtentorial region of the brain; in adults the proportion of tumours in this position is relatively small. Critchley[7], whose series included patients up to the age of seventeen years, found that 47·2 per cent. of his 125 tumours occurred below the tentorium. Cushing[9] in a critical review of the medulloblastomata reported that 70 per cent. of tumours in the first five years of life were subtentorial, whilst Armour[1] declared that in his experience this figure obtained for the first decade but that after the age of ten the incidence of supratentorial tumours rose rapidly until at the age of fifteen equal numbers were found above and below the tentorium. In a large series of cases in children up to the age of fifteen years Cushing found that the proportion of subtentorial to supratentorial tumours was two to one.

In the present series the localization of the sixty-two tumours verified at autopsy was determined. The relative frequency of tumours above and below the tentorium agreed almost exactly with the figures given by Cushing and quoted above. In forty-one of the sixty-two cases the tumour lay below the tentorium and in nineteen it lay above. In two cases, both of tuberculomata, a large mass was present in the cerebellum and had been diagnosed during life, whilst small masses were present in the cerebral hemispheres, in one case in the right parietal lobe, in the other in the left frontal lobe. Multiple tumours were present in four other cases. In two

of these they were all above the tentorium and in two all the tumours lay below it. One of the supratentorial cases was of particular interest. This was a tumour of both optic nerves and the chiasma with a separate tumour mass in the right frontal lobe. This case was shown during life at a meeting of the Neurological Section of the Royal Society of Medicine in 1924 by W. G. Wyllie and subsequently reported by him[19]. Another case which presented multiple tumours was one of extensive tuberculous disease in which a degenerating tuberculoma involved the whole of the basal nuclei on both sides, there being also a tuberculous mass in the left occipital lobe. Multiple tuberculomata were found in two other cases. In one, three tuberculomata were present in the cerebellum and one small mass in the floor of the fourth ventricle. In the other, the pons and cerebellum each contained one and in addition most of the lumbar region of the spinal cord was occupied by a caseous mass of degenerating tuberculous tissue.

The topography of the tumours is most simply expressed in tabular form (the six multiple tumours being excluded):—

Distribution of tumours in the brain.

Subtentorial.		Supratentorial.	
Mid-line cerebellar ...	13	Frontal and frontal-parietal	4
Lateral cerebellar	9	Parietal	1
Ponto-cerebellar	7	Temporal	2
Pontine	7	Occipital	2
Presenting at ponto-cerebellar angle but not localized exactly ...	2	Basal ganglia	3
		Suprapituitary	1
Tumours of fourth ventricle	1	Third ventricle	1
		Midbrain	2
		Crura cerebri	1

The absence of tumours of the pituitary region was surprising. Only one was present in the suprapituitary region. Cushing[8] traced no less than twenty pituitary or suprapituitary tumours amongst his 154 cases under fifteen years of age and Critchley[7] reported fourteen such tumours out of 125 cerebral tumours occurring below the age or seventeen years. It is of interest that there should be such an increase in the number of pituitary and suprapituitary tumours between the ages of twelve (which was the upper age limit of the present series) and seventeen years.

The vermis of the cerebellum was the commonest site of origin for a tumour. This observation merely confirms previous findings. In many cases the tumour remained localized to the vermis and involved neither lateral lobe. In other cases both the lateral lobes of the cerebellum and the pons were invaded. Other tumours, not arising in the vermis involved both the pons and one or both lobes of the cerebellum. These tumours were classified above as 'ponto-cerebellar.' Growths confined to one or other lateral lobe were recorded as 'lateral cerebellar.' The two tumours listed as 'presenting at the ponto-cerebellar angle' were difficult to localize with certainty. One was a haemorrhagic cyst which had burst,

much brain tissue in the vicinity of the ponto-cerebellar angle being destroyed; the other was a tumour of the choroid plexus involving the ventricles which presented on the under-surface of the brain in the situation described.

Tumours of the cerebral cortex were relatively uncommon, forming only one-seventh of the total number. They were of interest chiefly on account of their histological structure.

Histological differentiation

The number of tumours available for histological study was fifty-five. No material or sections could be traced in seven cases. From the excellent description of the histology of one case in which the sections could not be found, the case of a tumour of the optic nerves and chiasma reported[19] by Wyllie in 1924 there could be no doubt that this was a polar spongioblastoma. (The specimens and sections of an almost identical case were shown at a meeting of the Neurological Section of the Royal Society of Medicine in April, 1937, by the writer.)

The gliomata accounted for more than two-thirds of the tumours verified histologically. Forty-one of the fifty-four verified cases belonged to one of the sub-divisions of this group. The actual incidence was probably higher as four of the cerebellar tumours of which no sections were available were almost certainly gliomata.

The other tumours were six tuberculomata, four sarcomata (one of which was a melanotic sarcoma), two meningiomata, and one epithelioma of the choroid plexus. This preponderance of the gliomata confirmed other recent findings in children. Van Wagenen[17] remarked that the gliomata rather than the tuberculomata represented 50 per cent. of cerebral tumours in children, whilst Blacklock[6] made a histological examination of a hundred malignant tumours from all parts of the body which revealed no less than 20 per cent. as belonging to the glioma group. Cushing[8] in his series of 154 cerebral tumours in children under the age of fifteen classified 116 as gliomata.

The classification of gliomata by Bailey and Cushing[5] according to their histogenesis has allowed a certain parallel to be drawn between the appearance of the tumour under the microscope and its clinical course. This follows the accepted principle that the more primitive the cells of which the tumour is composed the more malignant it is and the shorter will be the duration of life. In the nervous system, however, another cogent factor has to be considered, the situation of the tumour. A tumour may consist entirely of well-differentiated cells and be eminently suitable for complete surgical removal but it may be present in a position to which surgical access is impossble, for example, deep in the pons or midbrain. The results of the histological examination of the present series of tumours clearly

illustrates this point. Benign gliomata were as common as the malignant types but owing to the position of many of the benign forms surgical removal would have been out of the question. This was particularly evident in the pons, where six out of the seven tumours present in this region were benign astrocytomata. Owing to their situation deep in the pontine-tissues and

TABLE 2.

POSITION OF HISTOLOGICAL TYPES OF TUMOUR IN SUBTENTORIAL REGION OF BRAIN.

	Mid-line cerebellar	Lateral cerebellar	Ponto-cerebellar	Pontine	Fourth ventricle
Medulloblastoma	7	2	2	0	0
Glioblastoma	0	2	1	1	0
Ependymoma	2	0	1	—	1
Astrocytoma group ...	2	3	1	6	0
Tuberculoma	0	1	0	0	0
Sarcoma	1	0	0	0	0

TABLE 3.

POSITION OF HISTOLOGICAL TYPES OF TUMOUR IN SUPRATENTORIAL REGION OF THE BRAIN.

	Fronto-parietal	Parietal	Parieto-temporal	Temporal	Occipital	Basal ganglia	Third ventricle	Mid-brain	Crus
Glioblastoma ...	0	1	0	0	0	0	0	1	0
Spongioblastoma ...	0	0	0	0	0	0	1	—	0
'Mixed glioma' ...	1	0	0	0	1	0	0		0
Astrocytoma group...	1	0	0	0	0	3	0		0
Meningioma ...	0	0	1	1	0	0	0		0
Sarcoma	1	0	0	0	1	0	0		1

their close proximity to vital centres they were inoperable. Tables 2 and 3 give the distribution in the subtentoral and supratentorial regions of the brain of the histological types. The gliomata are listed in descending order of malignancy (multiple tumours are excluded as they have already been mentioned).

Certain features of the histology of these tumours merit comment. The first is the high incidence of the most benign form of glioma, the astrocytoma. This tumour consists of well-differentiated neuroglial cells with fibrillar processes which are demonstrable by special stains. The tumour varies in cellularity; some forms are practically acellular (astrocytoma fibrillare) whilst some contain differentiating cells with fewer

fibrils (astrocytoma protoplasmatica). No attempt has been made in this study to separate the two forms as in many cases it was impossible to obtain material for special staining methods. Sixteen examples of an astrocytoma were encountered, whilst the two most malignant gliomata, the medulloblastoma and the glioblastoma, together totalled the same number (eleven medulloblastomata and six glioblastomata). The astrocytomata were nearly as common in the subtentorial region as the medulloblastomata and glioblastomata together, but it has previously been mentioned that the majority of these benign tumours were situated inaccessibly in the pons. In three instances the astrocytomata had the peculiar diffuse distribution designated ' diffuse gliomatosis of the pons.' In the cerebellum and ponto-cerebellar region the astrocytoma was only half as common as the more malignant forms. Bailey[1] in a large series found that 50 per cent. of cerebellar tumours were benign astrocytomata.

The occurrence of the malignant glioblastoma multiforme (formerly called ' spongioblastoma multiforme ') in six cases was rather surprising. This is predominantly a tumour of adult life and few examples have been recorded in children. Bailey and Cushing[5] reported that their youngest example was that of a child of twelve years. These tumours are said to occur almost invariably in the cerebral hemispheres (Bailey[2]). Bailey and Cushing[5] found only two in the cerebellum out of seventy-seven examples. As the name suggests, these tumours are remarkable for the polymorphism of their constituent cells. Degenerative changes are common and haemorrhage is frequent. By appropriate staining methods cells resembling phases in development of neuroglial cells from the early unipolar spongioblast to the fully developed astrocyte can be seen, though all stages in development can rarely be found in a single section. The presence of giant cells, often of enormous size, with many lobed nuclei is characteristic. They probably represent an early stage in degeneration. Fig. 3 shows the variation in size of cells and two giant cells in a glioblastoma of the midbrain from a boy of four-and-a-half years, and fig. 4 a huge giant cell in a glioblastoma of the pons in a boy aged seven years. Two of the glioblastomata in this series occurred in the cerebellum; one in the pons; one involved the pons and the cerebellum; one occupied the whole of the midbrain and one lay in the parietal lobe. The age incidence is given in table 4, but it is noteworthy that one occurred at the early age of fourteen months.

Four examples of ependymal tumours were found. One was small and confined to the fourth ventricle; two apparently occupied the whole of the vermis of the cerebellum and one had grown from the floor of the fourth ventricle into the pons and cerebellum. These tumours occur for the most part in the same situation as the highly malignant medulloblastoma and their differentiation is important as the ependymoma is amenable to surgical treatment whilst the medulloblastoma invariably recurs, even after apparently complete removal. Macroscopically the ependymoma generally appears whiter in colour, is firmer and has a more irregular surface than

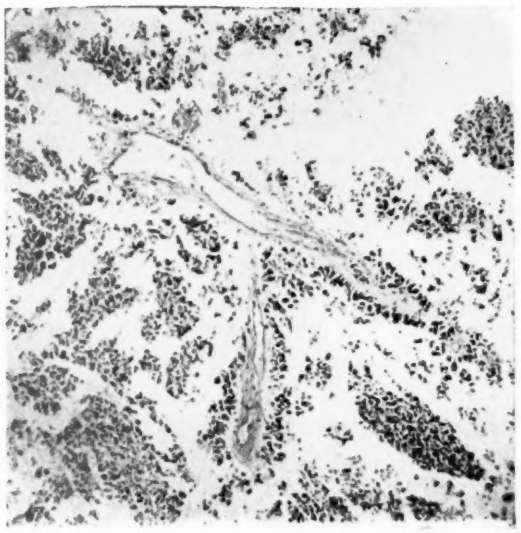

FIG. 1. x 50.—Low-power view of a medulloblastoma of cerebellum showing perivascular arrangement of cells with clear space between the cells and the vessel walls. (From a girl aged eleven years.) Stain: iron haematoxylin, Van Gieson.

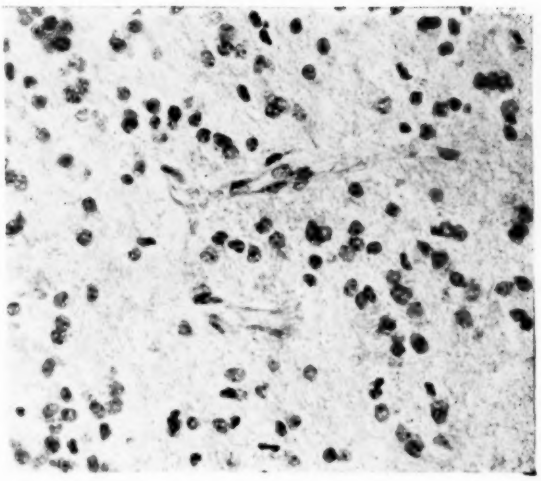

FIG. 2. x 220.—Section of an astrocytoma to show individual cells, all similar. The stroma is formed by fibrillar processes. (From the vermis of the cerebellum of a boy aged two-and-a-half years.) Stain: iron haematoxylin, Van Gieson.

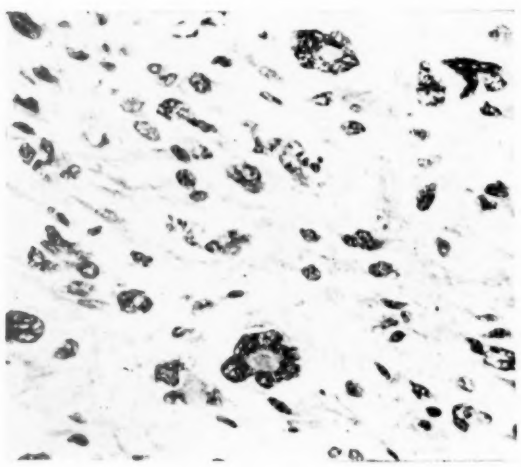

FIG. 3. x 340.—Section of a glioblastoma multiforme showing the variation in size and character of the cells. Two giant cells with lobed nuclei are present. (From the midbrain of a boy aged five-and-a-half years.) Stain: haematoxylin, eosin.

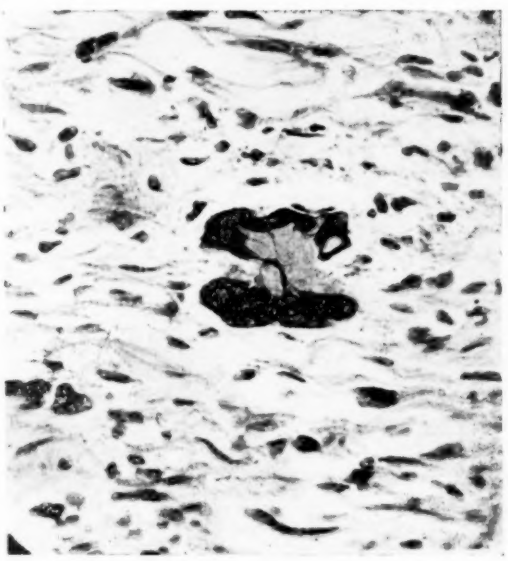

FIG. 4. x 320.—Section of a glioblastoma multiforme. An enormous giant cell undergoing mitosis occupies most of the field. Strands of chromatin can be seen between the dividing, lobed nuclei. (From a tumour of the pons in a boy aged seven years.) Stain: haematoxylin, eosin.

the medulloblastoma which is reddish-grey in colour, due to its vascularity. Microscopically the cells of the ependymoma are elongated with much cytoplasm prolonged into a thick process which is attached to the wall of a blood vessel. The nuclei are oval and the chromatin is finely divided. The elongated processes attached to blood vessels cause the cells to appear as if they radiate from the vessels. This appearance is described by Bailey as a ' pseudo-rosette ' (to distinguish it from the ' true rosette ' in which the cells radiate round a cavity lined by epithelium, as in neuroepithelioma of the retina). In the cytoplasm of many of these cells, near the nucleus, a group of small granules or rods may be seen. These granules are known as blepharoplasts and stain by neuroglial methods. Fig. 5 gives the general arrangement of cells in an ependymoma and fig. 6 is a high power view of a pseudo-rosette.

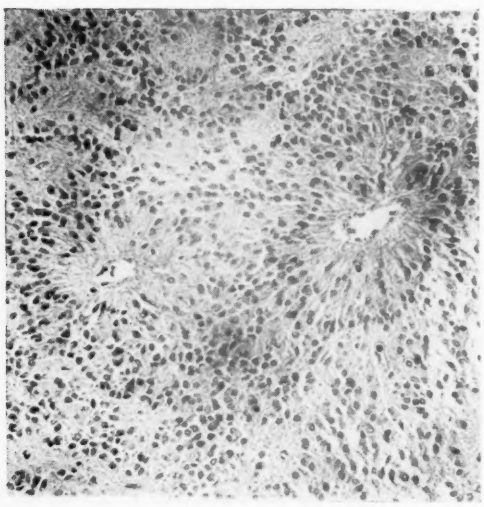

FIG. 5. x 100.—Low-power view of an ependymoma to show general arrangement of cells. Two ' pseudo-rosettes ' are present in the field. (From a mid-line tumour of the cerebellum in a girl aged four-and-a-half years.) Stain : haematoxylin, eosin.

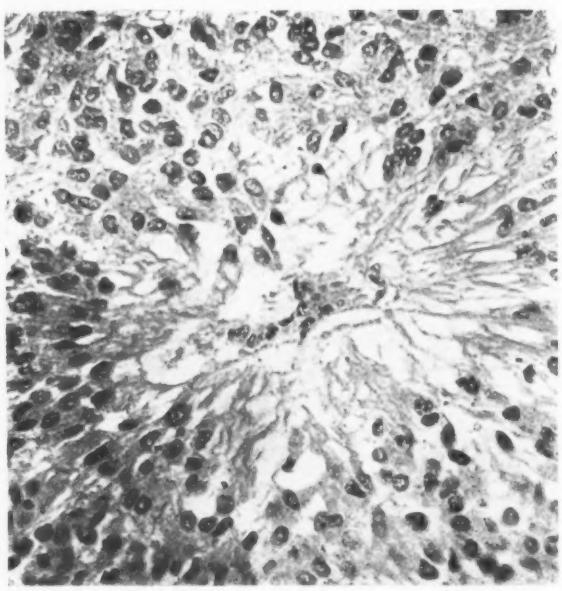

FIG. 6. x 320.—High-power view of a rosette from the same case as fig. 5. The cells radiate from the walls of the blood vessel to which their elongated processes are attached. Stain : Mallory's phosphotungstic acid haematoxylin.

The ependymomata are not very uncommon tumours in children. Five out of eight ependymomata in the series reported by Fincher and Coon[10] were in children under twelve years of age. Their cases were remarkable in that only two occurred in the region of the fourth ventricle; the three others were in the cerebral hemispheres. Gross[12] in reporting a series of nine cases of cerebral tumour in children under the age of two years was able to include three of ependymoma (one of which, aged one year and four months had previously been described by Fincher and Coon). In the present series there were two cases under the age of two years, one aged only five-and-a-half months.

The medulloblastomata presented no unusual histological features. These tumours are chiefly composed of small, undifferentiated cells with little cytoplasm, many of which show mitotic figures, but in some parts of the tumour more differentiated cells may be stained by silver impregnation methods. Many of the primitive cells are grouped around clear spaces in which a delicate fibrillar network can be seen (another type of ' pseudo-rosette '), whilst in other areas there is a definite perivascular arrangement of cells, a clear space being present between the cells and the wall of the blood vessel (fig. 1).

One tumour, a rapidly spreading growth of the third ventricle appeared to conform to the description of a spongioblastoma in this region given by Russell and Cairns[14] and was thus classified.

Four sarcomata occurred in the series. One of these (sarcoma of the occipital lobe in an infant of one year and ten months), was reported by Russell and Ellis[13]. Of the others, two were small round-celled sarcomata, one of which occupied practically the whole of the right frontal lobe and involved the dura extensively, whilst the other appeared to arise in the crura cerebri. Both were apparently primary. The fourth case was one of melanotic sarcoma, and presumably a secondary growth, but unfortunately the autopsy was limited to the brain and no note was made of the condition of the retina.

It was rather remarkable that only one solitary tuberculoma was found. This was a huge mass replacing the whole of the right lobe of the cerebellum. In one other case the mass in the cerebellum was large and only one as big as a pea was present in the right parietal lobe. These two cases and the case in which there was extensive destruction of the basal ganglia were operated upon for decompressions. None of these cases showed a tuberculous meningitis at autopsy. In only two of the six cases of tuberculomata was there a meningitis. In one of these a tuberculomata in the cerebellum was situated at the extreme tip of the posterior pole; in the other, one was present in the floor of the fourth ventricle. This finding does not confirm the assertion of Garland and Armitage[11] that the cerebral tuberculomata practically only give rise to symptoms when meningitis supervenes.

The age incidence of the various types of tumour was of interest as contrary to what was expected the benign tumours occurred at an earlier age than did the more malignant ones. Eleven out of the sixteen astrocytomata were in children under the age of five years; only two of the medulloblastomata fell into this age period. The actual age incidence of the histological types is given in table 4.

TABLE 4.

AGE INCIDENCE OF HISTOLOGICAL TYPES OF TUMOURS.

TYPE OF TUMOUR	0-1 YR.	1-2 YR.	2-3 YR.	3-4 YR.	4-5 YR.	5-6 YR.	6-7 YR.	7-8 YR.	8-9 YR.	9-10 YR.	10-11 YR.	11-12 YR.
Medulloblastoma ...	0	1	1	0	0	1	4	1	1	0	1	1
Glioblastoma ...	0	1	1	0	0	1	3	0	0	0	0	0
'Mixed glioma' ...	0	0	1	0	0	0	1	0	0	0	0	0
Spongioblastoma ...	1	0	0	0	0	1	0	0	0	0	0	0
Ependymoma ...	1	0	1	0	1	0	0	0	0	0	1	0
Astrocytoma group	2	1	2	3	3	2	1	0	1	0	0	1
Meningioma ...	0	1	0	1	0	0	0	0	0	0	0	0
Tuberculoma ...	2	0	0	1	0	0	0	1	1	1	0	0
Sarcoma	0	2	0	1	1	0	0	0	0	0	0	0
Epithelioma of choroid plexus	0	0	1	0	0	0	0	0	0	0	0	0

Comment

The main points to which attention was directed were the general incidence of cerebral tumours, the age incidence, the differentiation of histological types and their age incidence. The figures obtained for the autopsy rate was higher than was expected—2·2 per cent. of all autopsies during the fifteen year period under review being due to cerebral tumours. It was not possible to ascertain accurately the proportion of cases of cerebral tumour to the total admissions for this period. The large proportion of tumours which occurred at an early age was a surprising result and at variance with most of the series hitherto published. One reason for this may be that most of the literature on cerebral tumours in children recently published has come from neurological hospitals which young infants seldom reach. An analysis of the topographical distribution confirmed the observations of others. Twice as many tumours were present below the tentorium as above it. In children therefore the more primitive regions of the brain appear to be affected by tumour rather than the regions more recently evolved. On the same grounds it might be supposed that the tumours present would consist of more primitive, malignant cells than do those of adults. Actually this was not the case in this series. A slow-growing tumour with well-differentiated cells was as common as the more malignant types of tumour derived from nervous tissue. The hopelessness of these cases with benign tumours is due to their situation which all too often offers insuperable difficulties to a surgical approach. They kill by their site of election rather than by their nature or size. It might also be expected that

the more malignant types of growth would occur at earlier ages than those more benign. This was not so in the present series. The majority of the benign growths occurred before the age of five years, whilst only a small proportion of the malignant gliomata arose before the fifth year.

Summary

One hundred and two cases of cerebral tumour which occurred during the period 1921 to 1935 in children under the age of twelve years have been investigated. Over one-half of these occurred during the first five years of life. There was no difference in the sex incidence. The sixty-two cases which came to autopsy formed 2·2 per cent. of all post-mortem examinations during that period. Fourteen of the tumours verified at autopsy occurred during the first two years of life. Tumours were twice as common below the tentorium as above it. No tumours of the pituitary fossa were encountered and only one occurred in the suprapituitary region. Unfortunately sections from this tumour were not available. A histological study was made of fifty-five tumours. Two-thirds of these belonged to the glioma group. Well-differentiated gliomata were as common as the more malignant forms but occurred in situations inaccessible to surgical treatment. There were six examples of a malignant glioma, glioblastoma multiforme, a tumour which almost invariably occurs in the cerebral hemispheres of adults. In this series three were found below the tentorium. Four ependymal tumours were included in the series. One of these was in an infant of five-and-a-half months. The more benign gliomata occurred at an earlier age than did those of greater malignancy. Only one solitary tuberculoma was found. Excluding the small multiple tuberculomata found by careful search in cases of tuberculous meningitis (which are being reported elsewhere and are not included in this series) tuberculomata were rare tumours. There were only six examples to record, and in four of these (on three of which a decompression operation had been performed during life), there was no evidence of a meningitis either clinically or at autopsy.

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STUDIES ON THE RETENTION OF IRON IN CHILDHOOD

BY

JAMES H. HUTCHISON, M.B., CH.B., F.R.F.P.S.G.*
(From the Department of Medical Paediatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

The efficacy of iron therapy in nutritional anaemia, which has been shown to be of such common occurrence in infants and adults (Mackay[16]; Faber[6]; Davidson et al[5]; Fullerton[9]) is apparently dependent on the administration of large doses of iron if given orally (Heath[11]; Witts[31]). In this connection it is interesting to recall that the use of large doses was first advocated in 1832 by Blaud[1]. Only a small amount of the iron ingested goes to the formation of haemoglobin and there has been much speculation as to the reason why it has to be given in such large doses, and as to the fate of the remainder of the iron which has not been utilized in haemoglobin building. That the body can store large amounts of iron has been shown by Reznikoff, Toscani and Fullarton[24], who found that, after the administration of phenylhydrazine hydrochloride to a case of polycythaemia, there was a blood destruction equivalent to 2·1 grammes of iron without any extra excretion of this metal. Ramage and Sheldon[21], recovered as much as 50 grammes of iron from the tissues in a case of haemochromatosis. The necessity for the use of massive doses of inorganic iron salts has until recently caused many workers to doubt if iron deficiency is the sole factor in the etiology of the nutritional anaemias (Whipple and Robscheit-Robins[30]). Heath, Strauss and Castle[12] showed that the parenteral administration of iron in inorganic form resulted in 100 per cent. utilization, and because of this Fullerton[8] sees no reason to postulate the existence of another factor, and suggests that the necessity for large doses is dependent, among other things, upon imperfect absorption. There are, however, few observations regarding the absorption of iron, and the importance of further investigation on its fate after ingestion is obvious. With a view to throwing some light on this problem, a series of iron-balance studies has been conducted on in-patients at the Royal Hospital for Sick Children in Glasgow.

Method of investigation

The subject was given a diet of known iron content for a period of four days before the beginning of the experiment. Thereafter, for a period of seven days on the weighed diet, the faeces were collected for analysis; then ferrous sulphate was added to the diet in doses which amounted to 4 grammes

* This work was carried out during the tenure of a William McCunn Research Scholarship.

or 8 grammes of the sulphate, the equivalent of 803·45 milligrammes or 1606·9 milligrammes of iron per week, and the collection of the faeces continued. The ferrous sulphate was given in aqueous solution with the addition of glucose syrup to minimize oxidation as recommended by Parsons and Hawksley[19]. The iron content of the urine was neglected, as all workers agree that urinary excretion of iron is negligible (Tompsett[27]; Hunter and Brock[3]. Weekly determinations of the haemoglobin, red blood cells and colour index, were made in every case. The haemoglobin levels were determined by the Sahli method. The haemoglobinometer was standardized against blood, the iron content of which had been estimated, and it was found that a reading of 100 per cent. on the haemoglobinometer represented a haemoglobin content of 17·3 grammes per 100 c.c. blood. After completion of the study, examination of the gastric contents, following a test-meal, was carried out in every case by the Rehfuss method, a Ryle's tube being used for the aspiration of the gastric contents.

The total faeces for each period were placed in a porcelain evaporating dish (the weight of which was known), and treated with methylated spirits. Thereafter, the faeces were dried on a hot plate until constant weighings were obtained on three consecutive days, and the weight of the dried faeces thus obtained. The dried faeces were then finely divided by grinding in a mortar and stored in a stoppered glass jar. By calculating the iron content of aliquot samples of faeces from each period, the total iron output for each period was determined. The method used for determining the iron content of the faeces was that described by Taylor and Brock[26], in which sulphuric acid digestion makes possible the volumetric estimation of iron by the permanganate titration method of Margueritte (Treadwell and Hall). Before the beginning of the metabolism studies the method was tested thoroughly and found to be accurate and satisfactory.

Like all macromethods for the determination of iron in biological material, this method is time-consuming, each estimation taking about eight days. When to this is added the ten to fourteen days required for drying the faeces it is about three weeks from the end of any one weekly experimental period before the determination of the iron retention during that period can be estimated. This led to certain difficulties in planning experiments but could not be overcome by the adoption of any one of the many microcolorimetric methods for biological assay, because the errors entailed in those methods are greatly exaggerated when amounts of iron between 1 and 10 milligrammes are being estimated.

The results of iron balance studies which have been carried out on six patients over long periods are presented. The duration of the experiments varied from eight to sixteen weeks and comprised in some cases as many as sixteen weekly periods. Of these six patients, four gave normal or almost normal values for haemoglobin and red blood cells at the beginning of the metabolism studies, and the remaining two were cases of severe hypochromic anaemia. The findings of the normal and anaemic cases are discussed separately.

Results : Non-anaemic subjects

Case 1. E. S., a girl aged eleven years, was admitted to the wards with chorea minor. The iron-balance study, the results from which are shown in table 1, was begun after complete cessation of choreiform movements.

The first weekly period was in the nature of a control period during which no iron was administered apart from the small amount (37·87 milligrammes) contained in the food. Throughout the second, third, fourth, fifth and sixth periods, 4 grammes of ferrous sulphate (equivalent to 803·45 milligrammes of iron) were administered orally each week, the total iron intake of 841·32 milligrammes per period being the sum of the food iron and the inorganic iron given in the form of ferrous sulphate. The total iron output was not determined for the fourth and fifth periods. During the seventh, eighth, ninth and tenth periods the child received 8 grammes of ferrous sulphate (equivalent to 1606·90 milligrammes of iron) per week, the total iron intake during each period being 1644·77 milligrammes. After completion of the tenth period the administration of ferrous sulphate was stopped.

From table 1 it can be seen that this girl, who constantly presented a normal blood picture, retained remarkably large amounts of the iron administered: 72–87 per cent. of the total intake per period was retained when the weekly intake amounted to 4 grammes of ferrous sulphate, and from 27–76 per cent. of the intake with 8 grammes of ferrous sulphate. Another feature of interest is the wide variation of the retention of iron during different weekly periods. These differences are probably to be explained, in part, by the possibility that an apparently large retention during one period, may be due to constipation with accumulation in the bowel of non-absorbed iron, which being passed in the faeces of the next period produces an apparently small retention of iron for that period. Thus, when there was a positive iron balance of 1254·91 milligrammes during the ninth period, and a negative balance of 211·02 milligrammes during the tenth period, the amount of faeces passed during these periods were 39·62 grammes and 112·20 grammes respectively. This artefact could be abolished by the use of long periods and it is of interest and significance in this connection that Brock and Hunter[3] using three-day periods in contrast to the seven-day periods used in these experiments, found much larger variations in the retention of iron. From table 1 it is also apparent that when the administration of ferrous sulphate was discontinued on completion of the tenth period, re-excretion of some of the iron retained took place during the eleventh, twelfth and thirteenth periods. In brief, the total amount of iron retained by the child over the fourteen weeks was approximately 3·5 grammes. The normal iron content of a child of this age is about 1·5 grammes, so that presumably the body stores of iron were trebled in amount.

Case 2. A. C., a boy aged ten years, was admitted suffering from subacute rheumatism. An iron-balance study (table 2) was begun as soon as the sedimentation rate had fallen to normal. The first period was, as in the preceding case, a control period. From the second to the end of the seventh period 4 grammes of ferrous sulphate per week were administered, and from the eighth to the end of the twelfth period, 8 grammes

TABLE 1.

ABSORPTION AND RETENTION OF IRON IN A NORMAL SUBJECT.

E. S., AGED $10\frac{10}{12}$ YEARS. CHOREA.

WT.: 24·72 KGM. BLOOD VOLUME: $\frac{24{\cdot}72}{15}$ = 1·65 LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	HB. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS HB.	IRON (MGM.) RETAINED AS HB.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	37·87	4·08	33·79	90	90	5,100,000	871			
2	841·32	107·49	733·73	87	90	4,960,000	871	Nil	Nil	Nil
3	841·32	220·58	620·74	74	92	5,380,000	890	21	3·4	2·5
4	841·32	—	—	—	92	4,980,000	890	Nil	—	—
5	841·32	—	—	—	92	4,980,000	890	Nil	—	—
6	841·32	236·37	604·95	72	95	5,000,000	919	29	4·8	3·4
7	1644·77	699·03	945·74	57	95	4,970,000	919	Nil	Nil	Nil
8	1644·77	1177·26	467·51	27	95	5,190,000	919	Nil	Nil	Nil
9	1644·77	389·86	1254·91	76	95	4,960,000	919	Nil	Nil	Nil
10	1644·77	1855·79	−211·02	Nil	95	5,270,000	919	Nil	Nil	Nil
11	37·87	1631·62	−1593·84	Nil	95	5,040,000	919	Nil	Nil	Nil
12	37·87	783·77	−745·90	Nil	95	5,070,000	919	Nil	Nil	Nil
13	37·87	107·28	−69·41	Nil	95	5,020,000	919	Nil	Nil	Nil
14	37·87	23·58	+14·29	+37	95	5,130,000	919	Nil	Nil	Nil

TABLE 2.

ABSORPTION AND RETENTION OF IRON IN A NORMAL SUBJECT.

A. C., AGED $9\frac{1}{12}$ YEARS. RHEUMATISM.

WT.: 20·79 KGM. BLOOD VOLUME: $\frac{20 \cdot 79}{15}$ = 1·39 LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	HB. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS HB.	IRON (MGM.) RETAINED AS HB.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	39·48	105·13	−65·64	Nil	85	4,880,000	683			
2	842·93	410·21	432·72	51	85	4,570,000	683	Nil	Nil	Nil
3	842·93	948·09	−105·16	Nil	85	4,780,000	683	44	21·1	5·2
4	842·93	633·92	209·01	25	90	4,960,000	727	Nil	Nil	Nil
5	842·93	—	—	—	90	5,120,000	727	Nil	Nil	Nil
6	842·93	—	—	—	90	5,000,000	727	Nil	Nil	Nil
7	842·93	585·38	257·55	30	90	4,750,000	727	Nil	Nil	Nil
8	1646·38	1055·97	590·41	36	90	5,010,000	727	Nil	Nil	Nil
9	1646·38	1583·45	62·93	4	90	4,870,000	727	Nil	Nil	Nil
10	1646·38	1930·09	−283·71	Nil	90	5,230,000	727	Nil	Nil	Nil
11	1646·38	1577·74	68·64	4	90	5,160,000	727	Nil	Nil	Nil
12	1646·38	1644·80	1·58	0·9	90	5,020,000	727	Nil	Nil	Nil

TABLE 3.

ABSORPTION AND RETENTION OF IRON IN A NORMAL SUBJECT.

G. N., AGED $\frac{7}{12}$ YEARS. INFANTILE ATROPHY.

WT.: 4·68 KGM. BLOOD VOLUME: $\frac{4{\cdot}68}{15}$ = 0·312 LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	HB. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS HB.	IRON (MGM.) RETAINED AS HB.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	820·11	430·76	389·35	47	85	4,620,000	156			
2	820·11	207·12	612·99	75	85	4,660,000	156	Nil	Nil	Nil
6	820·11	317·65	502·46	66	85	4,950,000	156	Nil	Nil	Nil
7	16·66	−81·59	−64·93	Nil	85	4,730,000	156	Nil	Nil	Nil
8	16·66	12·91	3·75	22	85	4,740,000	156	Nil	Nil	Nil

TABLE 4.

ABSORPTION AND RETENTION OF IRON IN A NORMAL SUBJECT.

J. McE., AGED 1/2 YEARS. INFANTILE ATROPHY.

WT.: 5·94 KGM. BLOOD VOLUME: $\frac{5·94}{15}$ = 0·396 LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	HB. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS HB.	IRON (MGM.) RETAINED AS HB.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
*1	744·37	322·30	422·27	56	75	4,010,000	174			
2	821·09	—	—	—	70	4,490,000	163	−11	—	—
3	821·09	—	—	—	80	5,450,000	186	+23	—	—
4	821·09	612·05	209·04	25	85	5,150,000	197	11	5·3	1·3
5	821·09	641·00	180·09	22	90	5,100,000	208	11	6·1	1·3
6	821·09	730·79	90·30	11	90	5,100,000	208	Nil	Nil	Nil
7	821·09	626·04	195·05	24	90	4,750,000	208	Nil	Nil	Nil
8	17·64	104·72	−87·08	Nil	90	4,970,000	208	Nil	Nil	Nil
9	17·64	9·27	8·37	45	90					

* The total iron intake during the first period is less than those given for the other periods up to the seventh. This is due to the fact that the infant vomited two doses of iron during this period, and thus the figures given for this period are less accurate than is the case in the other periods.

TABLE 5.

ABSORPTION AND RETENTION OF IRON IN A CASE OF NUTRITIONAL ANAEMIA.

P. D., AGED 3 YEARS. NUTRITIONAL ANAEMIA.

WT.: 12 KGM. BLOOD VOLUME: $\frac{12}{15}$ = 0·80 LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	HB. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS HB.	IRON (MGM.) RETAINED AS HB.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	23·31	20·23	3·08	13	35	3,430,000	163			
2	826·76	346·80	479·96	58	39	3,870,000	196	33	6·9	4·0
3	826·76	385·89	440·87	53	52	4,360,000	244	48	10·9	5·8
4	826·76	339·32	487·44	59	63	5,040,000	295	51	10·5	6·2
5	826·76	245·76	581·00	70	78	4,980,000	365	70	12·0	8·4
6	826·76	178·29	638·47	77	85	5,290,000	399	34	5·3	4·1
7	826·76	584·64	242·12	27	87	5,000,000	405	6	2·5	0·7
8	835·51	812·61	22·90	3	90	5,070,000	422	17	73·9	2·0
9	835·51	676·18	159·33	19	90	5,070,000	422	Nil	Nil	Nil
10	835·51	1113·15	−277·64	Nil	90	5,010,000	422	Nil	Nil	Nil
11	835·51	523·91	311·60	37	90	5,050,000	422	Nil	Nil	Nil
12	32·06	390·41	−358·35	Nil	90	5,070,000	422	Nil	Nil	Nil
13	32 06	33·69	−1·63	Nil	90	5,010,000	422	Nil	Nil	Nil
14	32·06	44·79	−12·73	Nil	90	5,000,000	422	Nil	Nil	Nil
15	32·06	24·47	7·59	24	90	5,020,000	422	Nil	Nil	Nil
16	32·06	17·86	14·20	44	90	5,040,000	422	Nil	Nil	Nil

per week. The blood picture was normal throughout the period of observation. During the second period the retention of iron was equivalent to 51 per cent. of the intake, while during the third and tenth periods, on the other hand, there were negative balances of 105·16 and 283·71 milligrammes respectively. It is obvious that the total retention of iron for the duration of the study was proportionately much less than was seen to occur in case 1.

Case 3. G. N., aged seven months, was admitted with infantile atrophy. The results from the iron-balance study on this infant are shown in table 3. During the first six periods on metabolism the infant received orally 4 grammes of ferrous sulphate per week, the iron intake per weekly period being 820·11 milligrammes. The administration of ferrous iron was stopped during the last two periods of the experiment (that is the seventh and eighth), the iron intake of 16·66 milligrammes per period being derived in these periods from the food which consisted of cow's milk. The development of excoriation of the buttocks prevented the determination of the iron retention during the third, fourth and fifth periods. Table 3 shows that the infant retained large amounts of the iron ingested. The total iron retention in the body over the eight weeks of the metabolism study (at the rate shown in periods one, two and six) amounted approximately to the remarkable figure of 2·5 grammes which is several times the amount of iron normally present in the whole body of an infant at this age. An accumulation of such magnitude raises the question as the possibility of toxic effects resulting from saturation of the tissues with iron. No untoward symptoms were observed, and it is of interest to note in passing that a careful perusal of the literature has brought to light only one authentic case of toxic effects following the administration of iron (Hurst[13]).

Case 4. J. McE., aged eight months, was admitted with infantile atrophy. Table 4 summarizes the results obtained from an iron-balance study, lasting over a period of nine weeks. Throughout each of the first seven weekly periods 4 grammes of ferrous sulphate were administered orally. Thereafter the iron was omitted. This infant also retained large amounts of iron, although the retention did not approach the huge amounts recorded in case 3 in spite of the fact, noted in table 4, that the infant exhibited a mild hypochromic anaemia at the commencement of the study, whereas in case 3 high haemoglobin values were obtained throughout.

Results : Patients with hypochromic anaemia

Case 5. P. C., a boy aged three years was admitted suffering from a profound hypochromic anaemia. The haemoglobin was 35 per cent., red blood cells, 3,430,000 per c.mm., and colour index, 0·51. An iron-balance study was carried out while the boy was being treated with 4 grammes of ferrous sulphate per week. The results are tabulated in table 5.

In this case, as in the others, the iron-content of the circulating haemoglobin as noted in the accompanying tables, was calculated by taking the blood volume to be $\frac{\text{(body weight in kilogrammes)}}{15}$ litres, and the iron-content of the haemoglobin to be 0·335 per cent. (White House Conference[29]). In this way the iron utilized for the formation of the new haemoglobin could be estimated, and the percentage of the retained iron so used calculated with a reasonable degree of accuracy (table 5). It is observed that this patient retained a large percentage of the iron administered. It is also seen that during all the periods of observation only a small percentage of the

large total iron retention was utilized in the building of new haemoglobin, the remainder being stored presumably in the liver as inert metal as far as haemoglobin formation is concerned. This point is more forcibly brought home, if it is realized that between the first period and the end of the eighth period 2895·84 milligrammes of iron were retained, although the rise of 55 per cent. in the haemoglobin during that period represented the addition to an 0·8 litre circulation of only 259 milligrammes of iron (equivalent to only 9 per cent. of the total retention of 2895·84 milligrammes). These figures, obtained from observations over a much longer period, agree very closely with the figures published by Brock[2] for similar experiments on adults suffering from idiopathic hypochromic anaemia.

Case 6. J. C., aged ten months, presented, on admission to hospital, the picture of hypochromic anaemia of moderately severe degree. As in case 5 an iron-balance study was performed while the infant was under treatment for anaemia (table 6). In this case also the haemoglobin increase bore little relationship to the iron retained. The haemoglobin rose by 6 per cent. in the seven days of the second weekly period (blood examinations being performed on the last day of each period); whereas the amount of iron retained by the body in those seven days (528·73 milligrammes) would have allowed an increase to more than 100 per cent. if the iron had been fully utilized for haemoglobin formation. The total amount of iron retained by this infant, during the second, third, fourth, fifth and sixth periods on metabolism, that is, during the time taken for the haemoglobin to rise from 50 to 85 per cent., was enough to produce a rise in the haemoglobin of more than 17 per cent. per day during that same period of time. The actual daily rise in haemoglobin was only 1 per cent.

Relation of gastric acidity to retention

It has been shown by Heath[11] that the haemoglobin and reticulocytes respond better to a given dose of iron when the gastric secretion is normal; he therefore draws the conclusion that the 'absence of free HCl in the gastric contents probably is a factor in preventing the adequate absorption of iron.' Mettier and Minot[17] from a series of experiments with acid-buffered meat mixtures came to the following conclusions:—'The studies appear to indicate that soluble iron compounds are absorbed from the gastro-intestinal tract or utilized more readily for blood formation when administered with acid than with alkaline meals.'

With these facts and ideas in mind it was decided to perform a test-meal on every case at the completion of the iron-balance study. The accompanying six charts depict the results of the gastric analyses in the customary manner in the six cases already described. The numbers of the charts correspond to the cases to which they refer.

Scrutiny of the charts reveal certain interesting facts. Case 2 in which, it will be remembered, comparatively small amounts of iron were retained, showed a high gastric acidity. Case 3 which retained remarkably large amounts of iron over a period of eight weeks, showed not only the absence of free hydrochloric acid in the stomach under the conditions of the Rehfuss

TABLE 6.

ABSORPTION AND RETENTION OF IRON IN A CASE OF NUTRITIONAL ANAEMIA.

J. C., AGED $1\frac{0}{12}$ YEARS. NUTRITIONAL ANAEMIA.

WT.: 9·31 KGM. BLOOD VOLUME: $\frac{9{\cdot}31}{15}$ = 0·62 LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	HB. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS HB.	IRON (MGM.) RETAINED AS HB.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	18·18	5·62	12·56	61	50	4,580,000	182			
2	824·66	295·93	528·73	64	56	4,320,000	204	22	4·1	2·6
3	824·66	224·54	600·12	73	65	5,050,000	236	32	5·3	3·9
4	824·66	522·35	302·31	37	73	5,000,000	265	29	9·6	3·5
5	824·66	429·86	394·80	47	83	5,080,000	301	36	9·1	4·4
6	824·66	411·88	412·78	49	85	5,040,000	309	8	1·9	0·9
7	824·66	354·95	469·71	57	85	5,080,000	309	Nil	Nil	Nil
8	824·66	537·66	287·00	35	85	5,030,000	309	Nil	Nil	Nil

CHART I.

RESULTS OF GASTRIC ANALYSIS IN CASE 1.

E S. CHOREA.

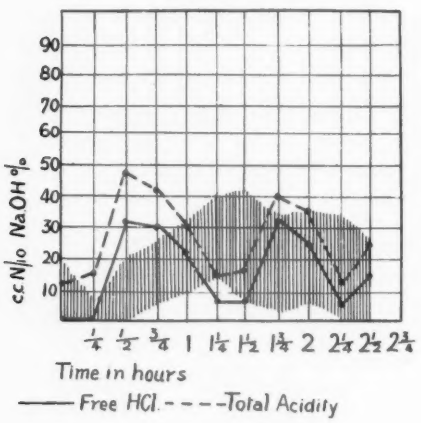


CHART II.

RESULTS OF GASTRIC ANALYSIS IN CASE 2.

A.C. RHEUMATIC INFECTION.

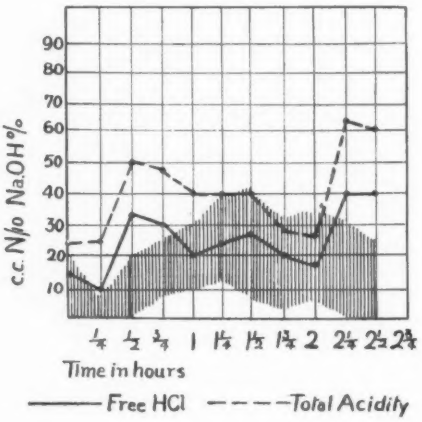
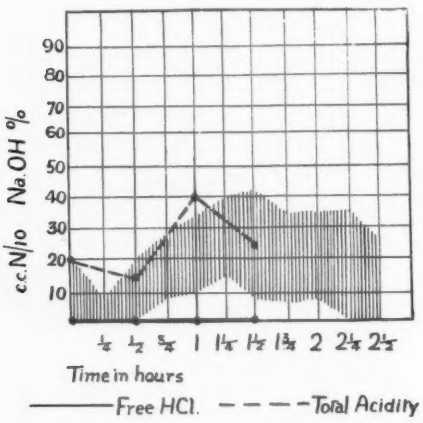


CHART III.

RESULT OF GASTRIC ANALYSIS IN CASE 3.

G.N. INFANTILE ATROPHY.



N.B.—After histamine injection there was no free HCl.

CHART IV.

RESULTS OF GASTRIC ANALYSIS IN CASE 4.

J.McE. INFANTILE ATROPHY.

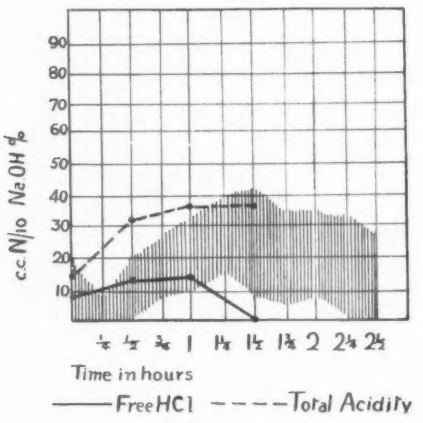


CHART V.

RESULTS OF GASTRIC ANALYSIS IN CASE 5.

P.D. NUTRITIONAL ANAEMIA.

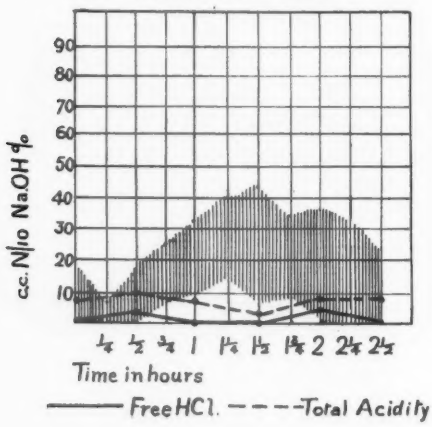
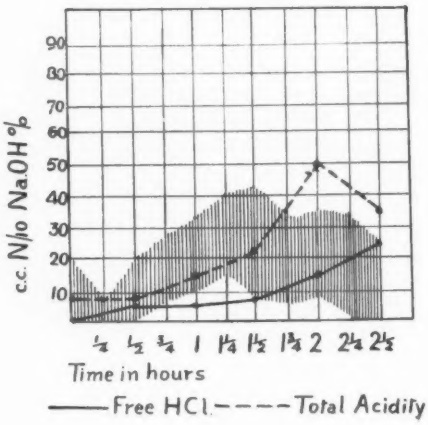


CHART VI.

RESULTS OF GASTRIC ANALYSIS IN CASE 6

J.C. NUTRITIONAL ANAEMIA.



test meal, but its absence even after stimulation of the acid-secreting glands with histamine.

This case, therefore, presented a true achylia gastrica in conjunction with the capacity to absorb large amounts of iron from the intestine. Cases 5 and 6 presented hypochlorhydria, a not uncommon finding in nutritional anaemia of infancy and childhood. (Hawksley, Lightwood and Bailey[10]; Ogilvie[18].) Case 5 absorbed enough iron in the first eight weeks of treatment to allow of an increase in haemoglobin of 13 per cent. per day and case 6 it will be recalled, absorbed enough iron to allow of an increase in haemoglobin of over 17 per cent. per day.

It is realized that there is hardly justification for drawing conclusions from so small a series of gastric analyses, but the results show that a low degree of gastric acidity does not preclude the ready retention of iron, which in the presence of anaemia may be used for haemoglobin building. Stewart[25] has approached this question from a more clinical aspect, and is inclined to attach less importance than other workers to the diminished gastric acidity as a factor in the etiology of the nutritional anaemias of infants (Faber, Mermod, Gleason and Watkins[7]). She concludes that it would appear extremely likely that the impairment of the gastric secretion is the result rather than the cause of the anaemia.

Discussion

The results of the metabolism studies carried out in this series of cases demonstrate clearly that the body is capable of retaining remarkably large amounts of iron administered in the inorganic state. Nor is it possible, in view of these results, to assume that the necessity for large doses of iron in the treatment of nutritional anaemia is dependent on the poor absorption of iron-salts from the intestine. Other workers (Brock and Hunter[3], Reimann, Fritsch and Schick[23]) have formulated similar conclusions upon the results of iron-balance studies in adults.

It would appear also that high rates of iron retention can be maintained over long periods, with resulting accumulation in the body of large amounts of iron. This was seen to be the case not only in the two patients showing anaemia, but also in three of the four non-anaemic patients. Even in case 2 considerable amounts of iron were retained, although the total retention for the duration of the study was proportionately much less than was seen to occur in case 1. The reason for this variation in the ability to retain iron is not obvious, but a similar observation has been made by Brock and Hunter[3] and Reimann, Fritsch and Schick[23].

Apart from the fact that for a period of three weeks after the administration of ferrous sulphate was discontinued case 1 appeared to re-excrete some of the iron retained, there is no definite evidence forthcoming from the above results to indicate that the capacity to store iron is limited. Case 5 after ten weeks' administration of 4 grammes of ferrous sulphate per week, had retained 3086·05 milligrammes of iron, of which only 259 milli-

grammes were used in the synthesis of haemoglobin, and only 372·71 milligrammes of iron were excreted after discontinuance of the administration of iron on completion of the eleventh period, before a positive iron-balance was again established during the fifteenth period. Cases 3 and 4 after retaining large amounts or iron over periods of six and seven weeks respectively, presented negative iron-balances for one weekly period only, after the stopping of massive iron-dosage; this can be explained by the fact that there is always a certain lag in the excretion of unabsorbed iron by the faeces.

It would appear, then, that the body is capable of storing in the tissues a large excess of iron over an indefinite period of time, and this again raises the question as to the possibility of toxic effects resulting. Polson[20] maintained a high iron content in the livers of rabbits over periods of one to four years by means of repeated administration of iron subcutaneously and intraperitoneally and found no evidence of hepatic cirrhosis or pancreatic damage in any of the rabbits. He concluded that excess of iron in the body over long periods caused neither liver cirrhosis nor haemochromatosis in rabbits, and it is unlikely that excess of iron is responsible for the hepatic and pancreatic lesions of human haemochromatosis. Cappell[4] after giving large doses of iron to mice and rats for as long as fourteen months found no evidence of haemochromatosis in the organs. The most outstanding contra-indication to the use of massive iron therapy can therefore be discontinued.

Once again it is necessary to seek an explanation of the need for such large doses, and of the inefficacy of smaller doses which only supply enough iron for haemoglobin formation. Brock[2] suggests the possiblity that large doses of iron are necessary in order to obtain a sufficiency of the copper impurity present in most iron preparations. He admits, however, that the claims of some workers, that the copper is effective as an adjuvant to iron in certain cases (Waddell, Hart, Steenbock and Elvehjem[28]; Lewis[15]; Josephs[14]) have not been generally confirmed. Against this theory also is the fact that ferrous sulphate used in the metabolism studies here reported contained less than 0·0005 per cent. of copper, so that no such interpretation can be put on the results of this series. Another possible explanation also advanced by Brock[2] is that large quantities of iron may alter the chemical composition of the intestinal contents and thereby increase the absorption of some undetected haemopoietic factor. It is admitted, however, that there is no real evidence as to the existence of such a haemopoietic factor.

There is another explanation, however, which can be advanced as a result of the foregoing metabolism studies. Assuming that iron once deposited in the tissues is not available for the regeneration of haemoglobin, unless it has been derived originally from the destruction of haemoglobin in the body, it follows that the great bulk of iron absorbed from the intestine during massive dosage with inorganic salts, would not be available as it would first find its way to the liver where it would be stored and thus

rendered inactive for haemoglobin synthesis. It is reasonable to suppose then, that only by giving massive doses of iron can the rate at which it is stored by the liver be overcome and the excess iron be pushed past the liver directly into the blood serum, from whence it may be utilized for haemoglobin formation. This would explain the 100 per cent. utilization of parenterally administered inorganic iron, as demonstrated by Heath, Strauss and Castle[12], such iron presumably being absorbed directly into the systemic circulation, whereas orally administered iron is absorbed into the portal circulation and stored in the liver. Of interest in this connection also, is the finding of Reicker[22] that the level of the serum iron can be raised by the administration orally of large doses.

It is probable, however, that the final explanation of the reason why it is necessary to administer iron in amounts far in excess of the actual requirements for the regeneration of haemoglobin will only be attained when knowledge regarding the chemical combinations in which iron occurs in the tissues is more precise, and also when a fuller understanding of the functions of the various components of the haemopoietic tissues is available.

Summary

(i) Observations on the retention of iron over long periods have been made in four non-anaemic and two anaemic children. The body is capable of retaining large amounts of iron. Only a small percentage of this iron is utilized for the synthesis of haemoglobin, even in those cases showing severe anaemia.

(ii) The necessity for giving large doses of iron by mouth does not depend on the poor absorption by the intestine.

(iii) No evidence was obtained that variations in gastric acidity influenced the retention of iron.

(iv) The suggestion is made that the iron stored in the liver is unavailable for haemoglobin formation, and only iron which overflows from the liver into the circulation can be utilized for haemoglobin formation. Massive doses are necessary to effect this.

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THE DEMONSTRATION OF THE TUBERCLE BACILLUS IN THE PULMONARY TUBERCULOSIS OF CHILDHOOD

BY

SETON CAMPBELL, M.A., M.B.

(From the Princess Elizabeth of York Hospital for Children, London.)

The diagnosis of pulmonary tuberculosis in children is notoriously difficult to establish, and this is in great part due to the rarity with which the tubercle bacillus is found. In the adult reliance is placed on the discovery of the bacillus in the sputum, and, unless this is done, the diagnosis must always remain in some doubt. The presence of the tubercle bacillus, if it can be demonstrated by any one of a variety of methods, clinches the diagnosis and can leave little doubt in the mind of even the most sceptical. Hence the finding of the bacillus must ever be a point of great importance, not only so that the diagnosis may be placed beyond doubt but in order that adequate treatment may be obtained; for the tuberculosis officer, armed with the fact that the bacillus has been seen, is able not only to provide more prolonged sanatorium treatment, but is better able to prevail on contacts to subject to examination. In the child, however, the obtaining of sputum for examination has always been a difficulty and there are many devices which have been introduced to overcome this.

In 1898 Mernier[1] made the first attempt to demonstrate the tubercle bacillus in swallowed sputum by means of stomach lavage, and this has within recent years become the favourite method. A high percentage of positive results has been reported by this method. Poulsen[2] obtained fifty-three positives out of 110 tuberculous children and Wallgren[3] examined the fasting stomach contents in thirty-seven children with erythema nodosum and positive Mantoux reactions, and was able to demonstrate the bacillus in seventeen instances, while Armand-Delille[4] reports 30 per cent. positive results in 110 tuberculous children. In 1904 Leonard Findlay[5] suggested attempting to obtain the sputum while it was in the pharynx and before it had been swallowed, and recently Nalbant[6] and Mishulow and her co-workers[7] have affirmed that repeated examination of the faeces will yield as high a percentage of positives as will stomach lavage.

Present investigation

The present communication reports an investigation of the relative advantages of the various methods of demonstrating the tubercle bacillus, and at the same time to attempt to establish the comparative value of the

various aids to diagnosis. A series of fifty suspect children were investigated as follows. A careful history was taken, especially as to contact with open tuberculosis, and a thorough physical examination was carried out, including radiology of the chest, while attempts to discover the tubercle bacillus were made by each of the following three methods:—

(i) Examination of the sputum when this was obtainable.
(ii) Examination of the faeces.
(iii) Stomach lavage and treatment of the contents by:—
  (a) Examination of a direct smear.
  (b) Culture on Lowenstein-Jensen medium.
  (c) Guinea-pig inoculation.

Those children were considered suspect in whom there was a history of contact with an open case of tuberculosis, those who were under four years of age and gave a positive Mantoux reaction, and those who on clinical grounds such as cough, wasting, pain in the chest or erythema nodosum suggested active tuberculosis.

The same procedure was adopted in all cases, and details of the results obtained are given in the following tables. The cases are arranged in order of age. Table 1 gives details of the fifty cases examined, while table 2 shows particulars of those cases which were found to be positive.

Discussion of results

Age.—A summary of the tables shows that fourteen of the fifty children were under three years of age and of these eight or 57 per cent. were bacilli carriers, while thirty-six were over three years and yielded only four positives (11 per cent.). These findings compare with Poulsen's[2] results in a series of 110 cases, in which sixty-two were under three years and of these forty-one or 66 per cent. were positive, while forty-eight were over three and gave twelve positives (25 per cent.). It would appear, therefore that, given a tuberculous child, the younger it is the more likely is it that the tubercle bacillus will be isolated by some method, although the technique is necessarily more difficult. This finding is in keeping with the belief that the disease is more severe and more widespread in the younger children; but it may really be due to the fact that the disease is at an earlier stage and therefore more likely to be active.

Contact.—Contact plays a large part in the spread of tuberculosis. Armand-Delille[8] from his statistics asserts that 60 per cent. of children with tuberculous parents develop the disease before the death of the parents. He further states that of those 60 per cent. fully two-thirds die from one of the acute forms, either miliary tuberculosis or meningitis, and that only one-third present any localization. In the present series of fifty cases, nine contact children were examined who appeared to be quite well; they were well nourished and their mothers were quite satisfied as to their progress. Of these nine children seven belonged to one family in which the mother

TABLE I.

SHOWING DETAILS OF ALL CASES INVESTIGATED.

CASE	AGE YEARS	COMPLAINT	CONTACT	PHYSICAL SIGNS	MANTOUX	SKIAGRAM	FAECES	SPUTUM	STOMACH WASHINGS		
									SMEAR	CULTURE	GUINEA PIG
1. M.P.	3/12	Cough	+	Râles	+	Consolidation	0	—	+	+	—
2. M.E.	3/12	Cough	—	Consol. r. apex ...	—	Miliary tub.	0	+	+	+	+
3. I.J.	6/12	Cough	+	Nil	+	Nil	0	—	—	—	—
4. G.D.	7/12	Axillary adenitis ...	+	Spleen enlarged ...	+	Miliary tub.	—	0	+	+	+
5. N.O.	7/12	Diarrhoea & vomiting	—	Rhonchi	+	Miliary tub.	0	0	—	+	+
6. W.C.	9/12	Loss of weight ..	—	Consol. r. apex ...	+	Consolidation	+	+	+	0	0
7. J.R.	1 2/12	Cleft palate ...	—	Nil	+	Nil	0	—	—	—	—
8. W.P.	1 6/12	Cough	—	Râles	+	Consolidation	—	—	—	—	—
9. M.A.	1 7/12	Vomiting	+	Râles	—	Nil	0	0	—	—	—
10. A.C.	1 8/12	Cough	+	Consol. l. apex ..	+	'Epituberculosis' ...	0	+	—	—	—
11. E.H.	1 8/12	Contact	+	Nil	+	Hilar shadow, enlarged	—	0	—	+	+
12. I.E.	1 10/12	Cough	+	Nil	+	Nil	—	0	—	—	—
13. P.W.	2	Cough	—	Consol. r. base ...	+	Consolidation	—	—	+	0	0
14. L.M.	2	Dysuria	+	Nil	+	Nil	0	0	—	—	—
15. K.H.	3	Contact	+	Nil	+	Nil	—	0	—	+	+
16. R.S.	3	Sore throat... ...	—	Consol. l apex ...	+	'Epituberculosis' ...	0	—	—	—	—
17. D.C.	3	Pain in knee ...	+	Nil	+	Nil	0	0	—	—	—

+ positive – negative 0 not done

TABLE I—*continued.*

Case	Age years	Complaint	Contact	Physical signs	Mantoux	Skiagram	Faeces	Sputum	Stomach washings		
									Smear	Culture	Guinea pig
18. R.S.	$3\frac{4}{12}$	Cough	—	Râles	+	Hilar shadow, enlarged	—	—	—	—	—
19. E.C.	$3\frac{1}{12}$	Pain in chest ..	+	Pleural effusion ...	+	Pleural effusion ...	—	0	—	—	—
20. J.M.	$3\frac{9}{12}$	Cough	+	Nil	+	Consol. r. base ...	0	0	—	—	—
21. R.M.	4	Diarrhoea	—	Mesenteric glands	+	Nil	—	—	—	0	—
22. M.B.	4	Loss of weight ...	+	Nil	+	Hilar shadow, enlarged	0	—	—	—	—
23. G.G.	$4\frac{9}{12}$	Pain in chest ...	—	Pleural effusion ...	+	Pleural effusion ...	0	—	—	—	—
24. G.S.	$4\frac{10}{12}$	Pain in chest ..	—	Pleural effusion ...	+	Pleural effusion ...	—	—	—	—	—
25. M.B.	4	Cough	+	Consol. r. base ...	+	Hilar shadow enlarged	0	—	—	0	—
26. V.R.	5	Loss of weight ...	—	Nil	+	Nil	0	—	—	—	—
27. P.M.	5	Cough	+	Râles	+	Nil	0	—	—	—	—
28. F.G.	$5\frac{6}{12}$	Cough	—	Rhonchi	+	Nil	0	—	—	—	—
29. L.W.	5	Cough	+	Consol. l. base ...	+	Consolidation	0	—	—	—	—
30. K.D.	6	Erythema nodosum	+	Erythema nodosum	+	Nil	0	0	—	—	—
31. C.M.	6	Contact	+	Nil	+	Hilar shadow enlarged	0	—	—	0	—
32. J.H.	6	Contact	+	Nil	+	Nil	—	0	—	—	—
33. J.C.	$6\frac{6}{12}$	Loss of weight ...	—	Nil	+	Nil	—	—	—	—	—
34. S.H.	7	Contact	+	Nil	+	Nil	—	—	—	—	—

+ positive − negative 0 not done

TABLE I—*continued.*

Case	Age years	Complaint	Contact	Physical signs	Mantoux	Skiagram	Faeces	Sputum	Stomach washings		
									Smear	Culture	Guinea pig
35. C.A.	7	Erythema nodosum	—	Erythema nodosum	+	Nil	0	0	—	—	—
36. J.D.	7	Chorea	—	Nil	+	Hilar shadow enlarged	—	—	—	—	—
37. D.W.	8	Contact	+	Râles	+	Hilar shadow enlarged	0	—	—	—	—
38. J.L.	8	Erythema nodosum	—	Erythema nodosum	+	Nil	0	0	—	—	—
39. F.C.	9	Cough	—	Nil	+	Nil	0	—	—	—	—
40. E.H.	9	Contact	+	Nil	+	Nil	—	—	—	—	—
41. L.H.	10	Contact	+	Nil	+	Nil	—	—	—	—	—
42. K.B.	10	Erythema nodosum	—	Erythema nodosum	+	Nil	—	—	—	+	—
43. S.N.	11	Erythema nodosum	—	Erythema nodosum	+	Nil	—	—	—	—	—
44. S.B.	12	Erythema nodosum	—	Erythema nodosum	+	Hilar shadow enlarged	0	—	—	0	—
45. D.A.	12	Tuberculous hip disease	—	Nil	+	Calcified areas... ...	—	—	—	—	—
46. A.H.	12	Contact	+	Nil	+	Nil	—	—	—	—	—
47. C.L.	12	Erythema nodosum	—	Erythema nodosum	+	Nil	0	0	—	—	—
48. R.W.	13	Loss of weight ...	—	Rhonchi	+	Nil	0	—	—	—	—
49. R.W.	13	Cough	—	Consol. r. base ...	+	Consolidation	—	+	+	+	—
50. V.M.	13	Cough	+	Nil	+	Consolidation	—	+	+	—	—

+ positive − negative 0 not done

suffered from open tuberculosis with positive sputum. All of the children in the family reacted positively to Mantoux's test although, as already noted, physical examination was negative. The youngest child showed enlarged uncalcified mediastinal glands on x-ray examination. Sputum was not obtained from the younger ones and was negative in the older, but from the stomach washings of the two youngest, aged three and one year and three months respectively, tubercle bacilli were grown in four-and-a-half weeks. Of the twelve cases which were proved positive (table 2) a history of contact was obtained in six instances (50 per cent.).

Physical signs.—It is worthy of comment that physical signs in the chest were not as valuable in indicating active mischief as might have been anticipated. But when the physical signs indicated a gross lesion, e.g., consolidation, the correlation with the presence of living tubercle bacilli in the sputum and more particularly in the younger children was fairly close. Of the eight children presenting consolidation on physical examination only five or 62 per cent. gave positive findings, but of the four under three years of age all were positive. Râles and rhonchi less seldom were evidence of active disease as only two out of nine cases gave positive findings, but again it may be stressed that of the three children under three years of age two were positive. Physical signs other than those in the chest may suggest active pulmonary disease. For example, in one child aged seven months an enlarged spleen was the only evidence of a miliary tuberculosis disclosed by radiology and confirmed by finding the tubercle bacilli in the stomach washings.

Seven patients with erythema nodosum, who gave a positive Mantoux test, were included in the series. In this condition some previous workers[3, 9] have recorded that the tubercle bacillus is found not infrequently in the stomach contents. All these children were over three years of age and in only one of them was the tubercle bacillus discovered. In this particular case physical and radiological examination of the chest was negative; indeed in this series of examples of erythema nodosum the only abnormal finding was the presence of a questionable increased hilar shadow in two instances. Three cases of pleural effusion were investigated but in none of these was the tubercle bacillus demonstrated in either the pleural fluid or the stomach washings.

Radiography.—It is generally recognized that radiology not infrequently discloses the presence of mischief in the lung not apparent on physical examination, and that the radiological evidence is usually much in excess of the physical signs. There are serious limitations to even this method of investigation. All shadows do not necessarily indicate tuberculous disease. There is the question of the significance of the enlarged hilar shadow and as McPhedran[10] has pointed out,small and even moderately enlarged caseous tracheo-bronchial glands, which form the majority of the lesions of these glands, are not demonstrable radiologically. It is only in the event of

TABLE 2

SHOWING DETAILS IN CASES WITH POSITIVE FINDINGS

CASE	AGE YEARS	COMPLAINT	CONTACT	PHYSICAL SIGNS	MANTOUX	SKIAGRAM	FAECES	SPUTUM	STOMACH WASHINGS		
									SMEAR	CULTURE	GUINEA PIG
1. M.P.	11/12	Cough	+	Râles	+	Consolidation	0	—	+	+	—
2. M.E.	3/12	Cough	—	Consol. r. apex ...	—	Miliary tub.	0	+	+	+	+
3. G.D.	7/12	Axillary adenitis ..	+	Spleen enlarged ...	+	Miliary tub.	—	0	+	+	+
4. N.O.	7/12	Diarrhoea & vomiting	—	Rhonchi	+	Miliary tub.	0	0	—	+	+
5. W.C.	9/12	Loss of weight ...	—	Consol. r. apex ...	+	Consolidation	+	+	+	0	0
6. A.C.	1 6/12	Cough	+	Consol. l. apex ...	+	'Epituberculosis' ...	0	+	—	—	—
7. E.H.	1 6/12	Contact	+	Nil	+	Hilar shadow enlarged	—	0	—	+	+
8. P.W.	2	Cough	—	Consol. r. base ...	+	Consolidation	—	—	+	0	0
9. K.H.	3	Contact	+	Nil	+	Nil	—	0	—	+	+
10. K.B.	10	Erythema nodosum	—	Erythema nodosum	+	Nil	—	—	—	+	—
11. R.W.	13	Cough	—	Consol. r. base ..	+	Consolidation	—	+	+	+	—
12. V.M.	13	Cough	+	Nil	+	Consolidation	—	+	+	—	—

calcification or if they are so much enlarged as to bulge outside the mediastinum that they will show up, and in these circumstances there is usually other evidence to be found in the lung field. In this series an enlarged hilar shadow alone was ignored unless there was evidence of a primary focus. But in spite of this restriction the bacillus was only found in one out of nine cases showing a Ghon focus and enlarged hilar shadow.

All the examples of miliary tuberculosis revealed the presence of the tubercle bacillus. Of seven cases showing in the skiagram consolidation of one or other lobe four or 57 per cent. were positive for the tubercle bacillus, but it is worthy of note that of the children over three years of age only 75 per cent. were positive whereas in children under three in whom consolidation was detected the tubercle bacillus was recovered in all cases. It would seem therefore that not only radiological evidence, unless unequivocal as in miliary disease, but also physical signs, are only of significance when taken in conjunction with the tender age of the child. The above facts are shown in tabular form below.

TABLE 3.

RADIOGRAPHY

RADIOLOGICAL APPEARANCES	NO. OF CASES	NO. OF POSITIVES	PER CENT. POSITIVE
Miliary tuberculosis	3	3	100
Consolidation	8	5	62
'Epituberculosis'	2	1	50
Hilar shadow enlarged	9	1	11
Pleural effusion	3	0	0
Nil	24	2	8

PHYSICAL SIGNS

PHYSICAL SIGNS	NO. OF CASES	NO. OF POSITIVES	PER CENT. POSITIVE
Consolidation	8	5	62
Râles or rhonchi	9	2	22
Erythema nodosum	7	1	14
Pleural effusion	3	0	0
Nil	21	3	14

Isolation of the tubercle bacillus

Faeces.—Mishulow[7], Nalbant[6] and others believe that examination of the faeces can yield as many positives as gastric lavage. Accordingly in twenty-six of the earlier cases the faeces were examined for the tubercle bacillus using the following technique:—

A portion of the faeces, preferably one containing blood or muco-pus, was picked up and emulsified in saline. This was centrifuged for thirty seconds to remove the coarser debris, the supernatant fluid was poured off and an equal quantity of 90 per cent. alcohol added. This was again centrifuged at high speed for three minutes. The supernatant fluid was again poured off, and from the sediment smears were made and stained for tubercle bacilli.

In this small series the results were not encouraging, as in no case was the tubercle bacillus found in the faeces when it could not be demonstrated in either the sputum or in the stomach washings, while in six cases examination of the faeces failed to reveal the bacillus when it was demonstrated in either the sputum or stomach washing. In the later cases therefore the faeces were not examined.

Sputum.—Findlay[5] described a procedure which consists of swabbing the back of the pharynx with a finger round which is a piece of gauze. If this is done during a fit of coughing so much the better, although the manipulation usually causes coughing, and the material obtained is spread on a slide and stained with Ziehl-Nielsen. In this series the procedure was only occasionally adopted but in one case was beautifully demonstrated and is worth considerable further trial. As Cowper has said that there must be at least 100,000 tubercle bacilli per c.c. to be detected, the value of working with a concentrated material such as sputum is therefore apparent. In the present series of fifty cases the sputum was obtained from thirty-five, but it will be noted that from the twenty cases under four years of age it was only obtainable in ten. Of the twelve positive cases (table 2) from which the tubercle bacillus was isolated by one method or another, the sputum was obtained in nine instances and in five of these the bacillus was demonstrated.

Gastric lavage.—All the children were subjected to stomach lavage, a process which they dislike intensely, and for this reason it was not repeated more often than was necessary.

Poulsen[2] in his fifty-three positive results demonstrated the tubercle bacillus at the first lavage in thirty-eight cases, in the second lavage in twelve, in the third in two cases, and in the fourth in one. Both he and Mishulow[7] agree that the search should be repeated a number of times if negative.

In the present series when the specimen from the stomach was abundant the lavage was not repeated. Many of the cases were only admitted to hospital for one night for the purpose, and so the lavage could not be carried out more than once. If, however, the specimen was inadequate, the patient's stomach was washed out again the following morning and the washings pooled.

The procedure was as follows:—On waking, the child was made to cough and, if any sputum was expectorated, this was kept for direct examination. A medium bore stomach tube was then passed by mouth and the contents washed out with 200 c.c. of distilled water. This was collected in a sterile bowl and delivered to the laboratory. Here a direct smear was made, part was treated for culture, and some was injected into a guinea-pig.

(a) DIRECT SMEAR. The stomach washings were poured into a Petri dish and examined on a dark background; a likely caseous area was picked up and a smear made. The method advocated by Armand-Delille and Vibert[11] of homogenizing the contents before making a smear as it increased their number of positives by 20 per cent., was not adopted on this work because it entails considerably extra time and this was not available. The direct smear as used was found of considerable value—as of the twelve positive cases the tubercle bacillus was demonstrated in this way in seven instances.

(b) CULTURE. For culture the stomach contents were treated in the following manner. One c.c. of the thicker mucus was taken up with a pipette into a test tube and to this was added 4 c.c. of 4 per cent. soda. It was then incubated at 37° C. for twenty minutes, and was shaken at five-minute intervals. By this time the mucus was dissolved and presumably the organisms, other than tubercle bacilli, were killed. It was then neutralized to phenol red with normal hydrochloric acid and centrifuged at high speed for one hour. The supernatant fluid was then decanted and the sediment sown on Loewenstein-Jensen medium. This medium was obtained commercially and was supplied in the screw-stopped bottles described by McCartney[12] which has the advantage of preventing evaporation over a long period of incubation. Subcultures gave rather a poor growth, and it was found that, once the growth had appeared, if the cultures were kept in the incubator the medium tended to liquefy and sink to the bottom of the tube.

The results with this medium and method of treating the stomach contents were gratifying. Of the positive cases ten were treated by this method and eight gave a growth of tubercle bacilli in from three to five weeks. Usually in three weeks a small wart-like, white or brownish, discrete growth appeared, followed by other similar ones. Smears showed typical tubercle bacilli. An emulsion from a typical growth was injected into a guinea-pig and a rabbit. The guinea-pig died in six-and-a-half weeks and tubercle bacilli were found in smears made from the spleen and lungs. The rabbit was killed after three months and tubercle bacilli were also isolated.

(c) GUINEA-PIG INOCULATION. For this the remains of the stomach washings were taken up into a centrifuge tube and spun for an hour. One c.c. was then removed from the top of the tube, the supernatant fluid decanted and the top c.c. added to the sediment. This is done on the principle that some tubercle bacilli are carried with a little mucus to the top of the tube during the centrifuging. The whole was made up to 5 c.c. with normal saline, and of this 0·5 c.c. was injected into the medial aspect of the guinea-pig's thigh. Magath[13] has described a method for accelerating the diagnosis in an infected pig. He injects the animal with 0·5 c.c. of old tuberculin four weeks after the inoculation, and finds that if infection has already taken place death will occur within forty-eight hours. If the animal does not die the chances of it having tuberculosis are about 1 in 30.

In fifteen of the present series of cases two guinea-pigs were injected from each case, and after a period of four weeks one of the animals was injected with 0·5 c.c. old tuberculin. In the cases subjected to this procedure death of the animals was not accelerated and both the injected and control pig had to be killed at the end of six weeks. This small number therefore does not confirm Magath's work.

The pigs were always killed at the end of six weeks and the positive ones usually showed gross tuberculosis. Sections of the spleen and sometimes of the glands and lungs, were cut in all cases, and only those which showed tuberculosis microscopically were considered positive.

Out of the twelve positive cases (table 2) animal inoculation was performed in ten, and from these the pig was infected in five instances. Twice in the course of a year epidemics of what on post-mortem examination proved to be capillary bronchitis or broncho-pneumonia, broke out and carried off a number of pigs. In some cases the inoculations were repeated, but in most the experiment had to be counted a failure if the pig died within three weeks of inoculation. This constitutes a serious disadvantage and is a point against relying entirely on animal inoculation for a diagnosis.

General discussion

In the efforts to demonstrate the tubercle bacillus in pulmonary tuberculosis the greatest proportion of success was obtained by culture of the stomach washings. Other workers have also obtained good results with culture on Loewenstein-Jensen medium. Evelyn Holmes [14], for example, obtains such a high proportion of positive findings in her series that she states that a negative culture in her hands has a considerable diagnostic value. Poulsen, Jensen and Husted[15] compare their results with the various methods of treating the stomach washings. From fifteen tuberculous patients they were able to demonstrate the bacillus in eleven instances. Five out of twenty-seven specimens were positive by direct smear (18·5 per cent.), but of the eighteen specimens cultured nine grew the tubercle bacillus (50 per cent.), while of the twenty-five animals inoculated nineteen were infected with tuberculosis (76 per cent.).

In the present series of fifty cases, out of the twelve examples in which the tubercle bacillus was eventually isolated, culture on Loewenstein-Jensen medium was carried out in ten instances and was positive in eight, i.e., 80 per cent. It should, however, be mentioned that of the above twelve positives, sputum was obtained in eight instances and of these five, or 63 per cent., disclosed the presence of the bacillus. In addition to the lower proportion of positive results from examination of the sputum the difficulty, indeed the impossibility, of always obtaining the sputum must be taken into consideration. Although, as previously mentioned, the children resent lavage of the stomach, the swallowed sputum can always be obtained.

Direct smear of the stomach washings was much less frequently positive than was culture. In the ten positive cases in which culture was carried out the organism was only found by direct smear in five, i.e., 50 per cent. as

against 80 per cent. by culture. Animal inoculation was also less frequently positive as in only five out of the ten cases, i.e., 50 per cent., was the organism isolated. The risk of the animals dying from intermittent disease, as well as the long time required for the test, are further drawbacks.

Summary

(1) In fifty children suspected of pulmonary tuberculosis the tubercle bacillus was found in sputum, faeces, or stomach washings in twelve instances.

(2) Sputum was obtained in nine of the twelve positive cases and in five of these the tubercle bacillus was discovered.

(3) Faeces were examined in a number of the cases but in no case was the bacillus found by this method when it could not be demonstrated by one of the others.

(4) In a direct smear of the stomach washings the tubercle bacillus was found in seven instances. In ten of the twelve positive cases the stomach washings were treated by guinea-pig inoculation and by culture, and the tubercle bacillus was isolated from the guinea-pig in five instances and by culture in eight.

(5) Owing to the possibility of epidemics amongst the guinea-pigs attention is drawn to the danger of relying entirely on this method of diagnosis.

(6) Whatever the lesion the tubercle bacillus is found most frequently in children under three, and this in spite of the greater difficulty of the examination at this period of life.

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CASE REPORT

GENERALIZED CUTANEOUS VACCINIA

BY

P. R. EVANS, B.Sc., M.B., CH.B., M.R.C.P.

(From the Children's Department, King's College Hospital.)

Generalized cutaneous vaccinia is a rare disease: Chalke[6] and Ellis[12] quote figures showing an incidence of from 1 case in 10,000 to 1 in 100,000 vaccinations. It may follow auto-inoculation, the integrity of the skin in these patients being usually impaired by some other skin disease, for example, eczema[20, 31] or seborrhoeic dermatitis[21]: in others the virus is inoculated by scratching[37]. When there is no pre-existing skin disease and lesions appear without scratching, implantation must be secondary to generalization in the blood. The notes which follow refer to this type.

Clinical record

The baby was a boy, aged 11 weeks, the first child of healthy parents. The father was vaccinated for the first time in 1929 when a severe reaction ensued. Vaccination of the mother was attempted in infancy but did not 'take.' She suffered from pyelitis for many months during pregnancy and labour was induced three weeks before term. Progress was uneventful, and on November 11, 1936, the boy was eleven weeks old and weighed 12½ lb. He appeared to be in perfect health. On this date he was vaccinated, two scratches 3 mm. long and 15 mm. apart being made over the left deltoid; one scratch just drew blood, the other did not. A gauze pad was placed over the scratches and fixed with strapping. This remained fixed and was not wetted in the bath at any time. The baby seemed very well for a week. On November 23 the pad was removed, two vesicles about 1 cm. in diameter were seen. They were powdered and a fresh dressing was applied. In the afternoon the child was fretful and seemed ill—the temperature was 100·8° F. This caused no anxiety as similar pyrexia occurs at this stage of normal vaccination (Ministry of Health Report[26]). Next morning the temperature was 100° F.; in the evening it had dropped to 99°. In the afternoon a small pimple was noticed in the adductor region of each thigh, one not opposite the other, and in the evening a greyish vesicle had appeared on the summit of each spot. The child was fretful, but seemed well. On November 25 the temperature was normal. Fresh spots were noticed from time to time during the day. They appeared as small red papules with greyish opalescent vesicles in their centres, the vesicle being about 1 mm. in diameter and the papule 3 mm. As the day went on the earlier-formed vesicles became yellow and opaque, and acquired areolae. Two became umbilicated, maturing in a few hours instead of the five or six days which are necessary for the full development of the lesion of primary vaccination.

The distribution of the pocks was: abdomen, one; right buttock, one; right thigh, two; left thigh, one; left calf, one; left foot, four; right hand, one; left hand, four. The primary pocks were scabbed and drying, but

FIG. 1.—Umbilicated pocks on legs and left foot.

FIG. 2.—Pocks in the left hand.

FIG. 3.—Primary vaccination surrounded by 'satellites.'

were surrounded by about twenty newly-developed vesicles, some grey and some yellow. The group was surrounded by a band of erythema 1 cm. in width, but the whole did not extend beyond the edge of the dressing.

On November 27 three fresh spots appeared on the left hand, and one or two more on the legs. The temperature was normal. On November 28 a sudaminous rash appeared on the back and on the neck. The infant was constitutionally well, he had taken his feeds readily throughout the illness and gained over 1 lb. in weight. On December 8 one spot on the finger was septic, but the rest had disappeared, leaving no sign except small pink areas of epithelium. The original vaccination was marked by a scab 1 cm. in diameter which fell on December 19th. Six months later two small scars could be seen at the site of the original vaccination, while the secondary lesions were barely visible as small areas of macular atrophy.

Discussion

The diagnosis is clear. There was no contact with variola, the symptoms were not severe, there was no rash on the face, and the infection was not transmitted to others. The umbilicated pustules and their peripheral distribution rule out varicella. Urticaria may occur after vaccination[33], but pustules do not develop. Pemphigus has been recorded as a sequel[4, 17, 28, 35], but the appearance and course of the disease is different. It is difficult to assert dogmatically that auto-inoculation did not play some part, but the care exercised by the mother, the facts that the dressing was not accidentally detached or immersed in the bath, the previous healthiness of the skin, the short time during which pocks appeared, and the fact that the child was too young to scratch, are strong evidence.

Generalized vaccinia may occur at any age. Lynch[22] has recorded a foetal case. Of twenty examples in the literature, twelve were in the first year of life, fifteen in the first decade, one in the second, two in the third, one in the fourth and one in the fifth. Probably the distribution may be explained by the frequency of vaccination in infancy. Primary vaccination is the usual antecedent, but Freeman's case[15] followed secondary, and Stewart's[36] tertiary vaccination. Many more cases have occurred in the first six months of the year than in the second in the northern hemisphere.

The prognosis is good except in infancy. Four deaths occurred in these twenty cases, all in the first year of life. Encephalitis does not usually accompany generalization, though it may possibly have been present in the patients described by Weichsel[39] and by Paisseau and Scherrer[30]. Secondary infection of the pocks may cause severe symptoms in a baby; vaccinial infection of the conjunctiva is to be feared because it may lead to corneal ulceration (Bedell[3]). Cutaneous scarring is negligible, probably because, as Dible and Gleave[10] have shown, the lesions are almost limited to the epidermis. (This is surprising in a blood-borne infection, but their patient also had visceral lesions.) In primary vaccination the dermis is infected, through a scratch or puncture, and the histological picture is different.

The disease is not communicated except by direct contact. The child's mother developed a vaccinial lesion on the breast in the case described by Oldham[29] and in that by Acland and Fisher[1]. In Milian's[25] case, the mother's cheek was infected, and the infection transmitted to a rabbit from this. Dible and Gleave[10] inoculated a rabbit with material from a secondary

pock, Hill and Ross[16] similarly transmitted the infection to a calf. Martin[24] did the same, and successfully vaccinated four human beings with the calf lymph. Huddleston[18] failed to vaccinate a child with lymph taken on the seventh day.

The lymph used does not seem to be at fault in these cases: it may be human or bovine, and lymph from the same source, used at the same time, produces normal vaccination in other patients. The defect probably lies in the individual whose cutaneous immunity is imperfect. Mere dissemination of the virus by the blood is not sufficient to cause cutaneous lesions, for Eckstein, Herzberg-Kremmer, and Herzberg[11] have been able to demonstrate vaccinia virus in the blood three to ten days after vaccination. This accords with the finding of the Ministry of Health Committee[26] that the spleen was palpable in two-thirds of a group of healthy adults one to ten days after vaccination. The spleen may be felt in patients with generalized vaccinia (e.g. Korach[19]) but not in every case.

Although the age incidence and prognosis in relation to age of generalized vaccinia differ from those of post vaccinial encephalitis, their incubation periods are similar. (For post-vaccinial encephalitis, see the Minstry of Health Committee's Second Report[27]; for generalized vaccinia see table 1.)

TABLE 1.

DAY OF APPEARANCE OF SECONDARY POCKS IN FORTY-THREE CASES OF GENERALIZED VACCINIA.

DAYS AFTER VACCINATION.	NO. OF CASES.	DAYS AFTER VACCINATION.	NO. OF CASES.	DAYS AFTER VACCINATION.	NO. OF CASES.
1	1	11	6	21	0
2	2	12	0	22	1
3	1	13	3	23	1
4	2	14	1	24	0
5	3	15	0	25	0
6	3	16	3	26	0
7	6	17	1	27	0
8	3	18	1	28	0
9	1	19	0	29	0
10	3	20	0	30	1

The lesion produced by vaccination matures on the eighth or ninth day, and normally the subject is thereafter immune for a long time. Further inoculation before the ninth day does, however, produce a true vaccinial lesion. This second lesion, as Bryce[5] recorded in 1809, is smaller than the first but proceeds though the same stages and arrives at maturity on the same day as the first pock. Trousseau[37] was familiar with this, but Cory[8] examined the phenomenon more thoroughly by performing daily vaccination on the same child: nine lesions were formed, but all matured on the ninth day, after which vaccination was unsuccessful. This was confirmed by von Pirquet[32]. Cory also vaccinated supernumerary digits, which were subsequently amputated; on revaccination a month later the second pock was found to mature in nine days, less the number of days the vaccinated

supernumerary digit had been allowed to remain on the body. He concluded that the body produced immunity to vaccination, and that the rapidity of maturation of a pock was a measure of the immunity when this was subtotal.

In generalized vaccinia the primary vaccination develops nomally, but immunity is defective, for in half the cases the incubation period was over nine days, and in over half of those with an earlier eruption spots continued to appear until after the ninth day. Accelerated maturation is seen in the secondary pocks. Six patients have been reported in sufficient detail to allow estimation of the time of maturation (table 2).

TABLE 2.

Author.	Secondary lesions.		
	Incubation period. Days.	Maturation period. Days.	Total. Days.
Huddleston[18]	3	5	8
Tyson[38]	5	½	5½
Freeman[15]	6	2	8
Korach[19]	7	1	8
Author's case	8	1	9
Stewart[36]	18	1	19

All matured rapidly, and in four the time taken was what would be expected if a second vaccination had been made a few days after the first, suggesting that the generalized virus reached the skin some days after primary vaccination. In one of the other cases the incubation period was eighteen days and the lesions matured in one day; in the other, rapid maturation in half a day was seen although the incubation period was only five days. Several unsuccessful attempts at vaccinating this child had been previously made, and Cory[8] observed that after such attempts an accelerated reaction was seen. He interpreted this as the result of inoculation with some soluble immunizing body from ' dead ' lymph. Craigie and Wishart[9] have shown that a soluble antigen does exist.

It may be concluded that generalized vaccinia is due to an inability of the patient to develop cutaneous immunity in the normal way, although accelerated maturation, the concomitant of developing immunity, is produced.

Treatment is directed at preventing abrasion and infection of the pocks —the same means should be used for secondary as for primary lesions. The question of whether or not to inject serum from a recently vaccinated person into the patient must also be considered. Lesions may continue to appear for as long as eighteen days, immune serum might prevent further generalization in the blood and so reduce this period, though it would probably have no effect on the established lesions. The disease is serious in the first year of life, and it would seem wise to treat infants in this way. Weichsel[39] has used maternal blood for this purpose.

Summary

An account of generalized cutaneous vaccinia in an infant is given. The disease is uncommon, it may occur at any age, and after primary, secondary, or tertiary vaccination. It is commoner in the first half of the year than the second. It may cause death in infancy, and may be transmitted by direct contact or animal inoculation. Its incubation period is similar to that of post-vaccinial encephalitis. It probably arises through a failure of the individual to develop cutaneous immunity. The treatment of infants with serum from a recently vaccinated person is advisable.

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STUDIES IN GASTRO-ENTERITIS

BY

EDMUND D. COOPER, M.D., F.R.F.P.S.
(From the Department of Paediatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

I.—CLINICAL ASPECTS OF INFANTILE DIARRHOEA

In spite of the great amount of work on the subject no satisfactory classification of the various gastro-intestinal disturbances of infancy has yet been agreed upon. All are more or less arbitrary, for no hard and fast line can be drawn between the several types of the syndrome. In this paper the simplest classification based on the clinical condition has been adopted.

Three hundred consecutive cases of diarrhoea and vomiting in children under two years of age admitted to the Royal Hospital for Sick Children between the years 1931 and 1934 have been studied. This series has been divided into two groups, viz.:—

1. Acute infantile diarrhoea and vomiting.
   (a) Severe type.
   (b) Mild type.
2. Chronic infantile diarrhoea.

The acute cases (severe type) comprise the type designated by various writers as anhydraemia[1], cholera infantum and toxicosis[2]. In the mild type are included patients in whom the symptoms of general systemic disturbance such as fever, dehydration and toxaemia were less marked than in the severe type but who suffered from diarrhoea and vomiting of varying degree of severity. The chronic cases are those showing wasting with frequent attacks of gastro-intestinal disturbance, the type designated by Marriott[1] as athrepsia. At times it was difficult to decide whether a patient was of the acute or chronic type but the general condition on admission to hospital, the presence of fever, collapse or dehydration and the duration of the illness were the main points taken into consideration.

In the total of three hundred patients ninety-eight belonged to the acute diarrhoea group (severe type). Two of these died within a few minutes of admission to hospital. One hundred and seven were of the mild type and ninety-five were classified as cases of chronic diarrhoea and vomiting.

Not all the patients were admitted with a history of diarrhoea and vomiting. In thirty the complaint was of convulsions, ' not thriving ' or

cyanosis; twenty were said to have vomiting and diarrhoea and thirteen diarrhoea without vomiting. In the patients with no history of alimentary disturbance definite evidence of diarrhoea or vomiting was forthcoming soon after admission; this with the absence of signs of disease elsewhere and, in some instances, with confirmatory evidence post-mortem justified the diagnosis of gasto-enteritis and their inclusion in this series.

Etiological factors

Age.—In the present series 65·2 per cent of the patients were under six months of age and only 12 per cent. over a year. The age period three to six months shows the highest incidence; possibly this is due to the fact that relatively few mothers can breast-feed their infants for more than three months and that after the age of six months artificial feeding is better tolerated. Parsons[3] in his series found that most of the patients were under the age of three months. On the other hand, in the United States it appears that the disease affects children over a year of age more commonly than those under a year[4] (table 1).

TABLE 1

AGE INCIDENCE

AGE	No. OF CASES	PERCENTAGE OF TOTAL	DEATHS	PERCENTAGE MORTALITY	
Under 1 month	19	6·3	14	73·6	
1-3 months	59	19·6	24	40·7	48·8
3–6 months	118	39·3	62	52·5	
6–12 months	68	22·6	29	42·6	
Over 1 year	36	12·0	13	36·0	

Season.—Most authorities are agreed that the disease is specially prevalent in the late summer and autumn months.

Thus Findlay[5] found in the severe epidemic of 1921 that 64 per cent. of the cases in that year occurred during July, August and September and Nabarro[6] in the same year found that the maximum incidence was in the third and fourth weeks of July and the first week of September. In America Marriott and others[7] reviewing a series of three hundred and twelve cases found that non-dysenteric diarrhoea occurred most frequently in the early autumn months and especially in those children whose nutrition had suffered during the summer season. They also noted that an appreciable number of cases occurred during the winter months.

The present series shows a similar seasonal incidence. The majority of the cases (68·8 per cent.) occurred during the months of June, July, August,

September and October and almost half of the series of three hundred cases occurred during the months of August, September and October (table 2).

TABLE 2

SEASONAL INCIDENCE

Month	No. of cases	Per cent. of total	Per cent. mortality	Month	No. of cases	Per cent. of total	Per cent. mortality
January ...	8	2·6	50·0	July ...	33	11·0	42·4
February ...	10	3·3	60·0	August ...	47	15·6	51·0
March ...	13	4·3	38·4	September	46	15·3	41·3
April ...	12	4·0	66·6	October ...	47	15·6	31·8
May ...	19	6·3	52·6	November...	22	7·3	63·6
June ...	34	11·3	61·7	December...	9	3·0	22·2

Social conditions.—It is well-known that the disease is rare in the upper grades of society and that it is extremely prevalent in the slums of cities. Most of the present series of patients came from slum dwellings although this does not necessarily prove the rarity of the condition in the children of the well-to-do for when housing conditions are good the necessity for hospital treatment is often unnecessary. Overcrowding is probably an important etiological factor; 36 per cent. of the present series came from families of five or more children (table 3).

TABLE 3

RELATIONSHIP OF INFANTILE DIARRHOEA TO SIZE OF FAMILY

Children in family	No. of cases	Percentage of total
1	58	21·5
2	48	17·7
3	42	15·5
4	25	9·3
5 or more ...	97	35·9
No data	30	—

Feeding.—It is well recognized that artificial feeding plays a major rôle in the development of infantile diarrhoea. In Findlay's[5] series of three hundred and twenty cases only 9 per cent. were breast-fed. In the present series two hundred and ninety were artificially fed, nine breast-fed and one partly bottle and partly breast-fed prior to admission. Thus only 3 per cent. of the cases were breast-fed.

Symptoms

Of the three hundred patients, twenty-four had a history of illness of one day's duration and half had suffered from alimentary disturbance for more than a week. Others again had a history of intermittent diarrhoea and vomiting but on admission were so acutely ill that they were classified as acute cases (table 4). Dehydration, toxicity and cyanosis are the three

TABLE 4

DURATION OF ILLNESS

DURATION OF CONDITION	NO. OF CASES	PERCENTAGE OF TOTAL	PERCENTAGE MORTALITY
1 day	24	8·1	54·1
1–3 days	34	11·4	41·1
3–7 days	91	30·6	45·0
Over 7 days	148	49·9	53·4
Not recorded	3	—	—

danger signs. All the acutely ill patients showed one or more of these. In the mild type these signs were much less evident while in the chronic type without exacerbation dehydration was absent (table 5).

TABLE 5

SEVERITY OF CONDITION ON ADMISSION

TYPE OF CASE	CLINICAL CONDITION	NO. OF CASES	PER CENT. OF TOTAL	PER CENT. MORTALITY
Acute (severe) ...	Severe dehydration	38	12·0	71·3
	Cyanosed and ill	22	6·8	85·0
	Toxic and dehydrated	36	11·4	73·5
Acute (mild) ...	Moderate dehydration	40	13·7	47·5
	Slight dehydration	67	22·8	37·3
Chronic	Ill but not dehydrated	48	15·8	48·0
	Not ill, no dehydration	47	15·7	19·1
Acute	Died before admission	2	0·7	—

Fever.—One hundred and forty patients had a greater or less degree of fever, and in sixteen the temperature was subnormal; these latter were acutely ill, with all the signs of severe collapse (table 6).

TABLE 6

TEMPERATURE (RECTAL) ON ADMISSION TO HOSPITAL

TEMPERATURE	NO. OF CASES	PERCENTAGE OF TOTAL
Sub-normal	16	5·3
98° — 99° F.	30	10·0
99° — 100° F.	112	37·3
100° — 102° F.	100	33·3
Over 102° F.	40	13·3
Not recorded	2	0·7

Finkelstein[8] has suggested that the fever is partly due to high carbohydrate diet and partly to negative water balance. Marriott[9] although admitting the possibility of negative balance as a cause lays much stress on parenteral infection. Schoenthal and Morton[10] favour the view that the fever in many cases arises from water depletion and demonstrated in a normal infant that it can be produced by limiting the fluid intake.

Parenteral infections. It is well known that infections outside the alimentary tract are commonly met with in infants suffering from diarrhoea and vomiting. To what extent they are causative factors in the production of the disease is open to doubt. Karelitz[11] and Marriott and others[7] favour the view that such infections play an important part in the etiology. The former showed that 50 per cent. of the patients in his series and the latter that 83 per cent. suffered from some form of parenteral infection. Of the present series one hundred and twenty-two (40·6 per cent.) had some form of parenteral infection (table 7), otitis media being by far the most common.

TABLE 7

INCIDENCE OF PARENTERAL INFECTIONS

PARENTERAL INFECTIONS	NO. OF CASES	PER CENT. OF TOTAL	PER CENT. MORTALITY
Otitis media	78	26·0	42 3
Bronchopneumonia	9	3·0	88·0
Pyuria	11	3·7	73 6
Furunculosis	5	1·7	60·0
Umbilical sepsis	3	1·0	66·6
Bronchitis	4	1·3	50·0
Throat infections	1	0·3	—
More than one infection	11	3·7	72·7
Total	122	40·7	52·0

Many of these patients, however, showed no evidence of parenteral infection on admission but developed the condition later. The possibility that the relatively low incidence of parenteral infection in the present series might be due to the fact that some were missed on clinical examination was recognized but as it is shown later there was no great discrepancy between the incidence arrived at by clinical and by post-mortem examination.

Clinically 40 per cent. were found to have parenteral infection while at post-mortem examination 48 per cent. showed this. Admittedly the condition was missed in a few cases but when it is borne in mind that more of the patients with parenteral infection died than those without this complication it would seem that the incidence arrived at on clinical grounds is probably fairly accurate.

Mortality

The mortality rate for the three hundred patients in the present series was 47·2 per cent. In the acute type with severe symptoms it was 76·6 per cent. and in the mild type 41·1 per cent.; in the chronic group it was 33·7 per cent. (table 8). The death rate among the acute cases does not compare favourably with the figures for similar cases given by other workers[12] except those of Hartman[14].

TABLE 8

MORTALITY RATE

INFANTILE DIARRHOEA	NO. OF CASES	PER CENT. MORTALITY	TOTAL MORTALITY PER CENT.
Acute (a) severe type	98	76·6	
(b) mild type	107	41·1	4.72
Chronic type	95	33·7	

Age.—As a general rule it may be said that the younger the child the greater the risk of death. In this series the mortality rate in the first year of life was 48·8 per cent. and in children in the second year 36 per cent. In infants under one month it was 73·6 per cent. These figures demonstrate the seriousness of the prognosis in all infants and especially in the very young (see table 1).

Duration of symptoms.—The highest mortality occurred among the patients admitted with acute symptoms of only one day's duration and those with a history of illness of more than one week's duration showed only a slightly lower mortality rate. Probably the acuteness of the symptoms determined the early admission to hospital of some of the patients and it is likely that the resistance of many of the infants who had been ill for a week

or more had been impaired by prolonged gastro-intestinal disturbance (see table 4).

Parenteral infection.—It might be expected that the mortality rate would be highest among those patients with some infection outside the alimentary tract; the figures presented demonstrate this but not as strikingly as might be expected. Of one hundred and twenty-two cases showing parenteral infection sixty-four died giving a death rate of 52 per cent. compared to a rate in the uncomplicated cases of 43·7 per cent. The reason that a higher mortality rate was not met with among patients with parenteral infection was probably because otitis media, by far the commonest infection, did not seem to prejudice the outlook. Bronchopneumonia and pyuria which occurred with comparative rarity were the killing complications (see table 7).

State of nutrition.—Taking the percentage of expected weight for the age as a measure of the state of nutrition it will be seen from table 9 that a

TABLE 9

PERCENTAGE OF EXPECTED WEIGHT ON ADMISSION

PERCENTAGE OF EXPECTED WEIGHT	NO. OF CASES	PERCENTAGE MORTALITY	TOTAL MORTALITY PER CENT.
100 or over	17	23·3	36·5
90–99	30	40·0	
80–89	56	35·7	
70–79	78	35·8	
60–69	53	53·0	65·0
50–59	27	77·7	
40–49	11	81·8	
Under 40	3	100·0	
Not tabulated	26	—	—

large number of the cases showed a greater or less degree of malnutrition; indeed only forty-seven of them were within ten per cent. of the normal weight. No doubt in a considerable number nutrition had been interfered with by repeated attacks of gastro-intestinal disturbance but many of the patients classified as acute, whose symptoms had been present only for a few days, were badly nourished.

It will be seen from the table that the death rate among the undernourished was higher than that observed in those who were more nearly of normal weight. The group of infants who were within 30 per

cent. of the normal weight showed a death rate of 36 per cent. while those who were less than 70 per cent. of their expected weight showed a death rate of 65 per cent. Fleming has found that the state of nutrition influences the mortality rate in primary pneumonia in a similar way (personal communication).

Pathology

It is recognized that the post-mortem findings sometimes show only slight evidence of pathological change in the various organs[5, 6]. In some patients with severe and acute illness only slight erythema of the bowel may be apparent while in others with less acute symptoms the bowel may exhibit marked inflammatory changes. In the more severe cases, however, definite evidence of some fatty changes in most of the vital organs such as the liver, kidneys and heart may almost always be seen. The lesion most frequently found is a varying but at times extreme degree of fatty change in the liver.

Eighty-seven cases of the present series came to post-mortem examination; to these are added four cases of pyloric stenosis in which diarrhoea and vomiting developed after operation. The only parenteral infections disclosed post-mortem and not recognized before death were several cases of terminal bronchopneumonia and a few cases of otitis media. The post-mortem results show that in forty-four of the series there was no parenteral infection detected. Twenty patients were found to have pneumonia which in nine cases was terminal. In the remaining twenty-seven a variety of infective complications was found—otitis media, pyuria, sinus thrombosis. In the forty-seven patients with definite evidence of parenteral infection it was impossible except in nine cases of terminal bronchopneumonia to decide whether the condition had occurred prior to the development of the alimentary symptoms or whether it was of later onset. As others have found, so in this series the degree of inflammatory reactions shown by the bowel did not in many instances bear any relationship to the severity of the symptoms[15]. Fatty change in most of the organs, especially marked in the liver, was commonly found[6].

Treatment

The high mortality rate from gastro-enteritis in infancy emphasizes the importance of any measures calculated to prevent its occurrence. The etiological factors concerned in this condition are numerous but one stands out above all others, viz., artificial feeding, for in the vast majority of cases (97 per cent. in the present series) the infants are artificially fed. It would appear therefore that breast-fed infants are almost immune and that by increasing the use of breast feeding the incidence of the condition would be greatly diminished. When artificial feeding cannot be avoided the greatest attention must be paid to nursery hygiene. With education in

this, better housing and improved facilities for the preparation of the infant's food it can be confidently predicted that there will be great reduction in the incidence of the disease.

Owing to the varying degrees of severity in the individual cases of the present series it is impossible with the data available to make a reliable comparison between the various types of treatment that have been utilized. All the patients admitted to the wards with a history of alimentary disturbance or exhibiting the signs and symptoms of such a condition were given as a routine bowel and stomach lavage provided they were not too ' shocked ' and nothing but water or saline by mouth for periods varying between six and twelve hours. Stomach lavage was often found to be successful in controlling vomiting.

Administration of fluid. — Although the figures presented in a succeeding paper do not indicate any striking loss of water from the tissues, it should be emphasized that there may be a considerable loss of water from the body without much alteration in the water content of the tissues. In addition it is important to remember that there is clear evidence of loss of water from the plasma as indicated by a considerable rise in the serum proteins and of accumulation of waste products. Accordingly there is ample justification for the administration of fluid which has so long held an important place in the therapy of acute gastro-enteritis. The added fluid diminishes the concentration of the blood and thus by lessening its viscosity eases the circulation and promotes increased renal activity. This together with the increased interchange between intra- and extra-vascular fluids facilitates the excretion of waste products the accumulation of which almost inevitably leads to acidosis and toxaemia.

The nature of the fluid administered seems within limits to be a matter of little importance. Normal saline is certainly the most easily procured. Hartman[14], however, prefers his buffer lactate solution. In the present series there was little difference between the therapeutic effects of normal saline and buffer lactate, a similar experience to that of Hoag and Marples[16]. There has not been a sufficient number of patients treated with the continuous intravenous drip method to make a useful statement as to its efficiency compared with single or repeated parenteral administration of fluid.

In cases of chronic infantile diarrhoea an important consideration is the improvement of general nutrition which is so often poor. There should be no hesitation in giving glucose solution intravenously for by this means it is possible to provide a readily-utilized food. In this type of case parenteral infection often plays an important part and such infections as otitis media and pyuria should be carefully watched for and adequate treatment adopted. In all patients in whom otitis media was detected, paracentesis of the tympanum was performed. It is impossible from examination of the case records to state if any benefit resulted from this procedure but in many cases a reduction in temperature followed the paracentesis.

Blood transfusion.—The place of blood transfusion in the treatment of diarrhoeal diseases of infancy is still disputed. Karelitz and Schick[13] and Johnston[17] have advocated its general use whereas Marriott and others[7] condemned it. Certainly when there is already marked blood concentration the transfusion of citrated blood may, and often does, result in further increase in the plasma protein percentage and intensification of the anhydraemia. In a series of eighteen patients who received one or more blood transfusions the results were poor but it must be admitted that they afford no real argument against its use since it was almost exclusively in the infants who were very ill that this form of treatment was employed. Blood transfusion, if it has a place in the treatment of infantile diarrhoea, is probably of greatest use in chronic cases when there is malnutrition; in such a patient it would appear that a blood transfusion while not a specific cure, may turn the scale in a favourable direction.

Summary

1. The clinical findings in three hundred cases of diarrhoea and vomiting in infancy are reviewed.

2. Artificial feeding appears to be the most important etiological factor.

3. Parenteral infection was present in 40 per cent. of the cases; it did not have as marked an influence on the mortality rate as might be expected.

4. The mortality rate varied inversely with the age and state of nutrition.

5. The morbid anatomical changes in the bowel found post mortem did not in many cases bear any relationship to the severity of the symptoms.

6. The value of administration of fluid in the treatment is emphasized.

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II.—CHEMICAL CHANGES IN THE BLOOD IN INFANTILE DIARRHOEA AND THE EFFECT OF INTRAVENOUS ADMINISTRATION OF FLUID

Although there is almost certainly some mechanism in the body which in most circumstances maintains a constant blood volume and concentration it is well recognized that great loss of body fluid or acidosis, or both, may upset this mechanism and lead to loss of water from the blood and increased concentration of its solid constituents[1]. In gastro-enteritis of infancy when the signs of dehydration may be severe it is probable that the blood as well as the tissues participate in the water loss. It is also well-known that the administration of fluid to patients with gastro-enteritis occupies an important if not central position in the therapeutic attack. In the present work an attempt has been made to study some of the changes that take place in the composition of the blood and to examine the effect of administration of fluid by intravenous injection of normal saline solution.

Unfortunately for various reasons it was not feasible to estimate blood volume directly; instead the concentration of blood constituents was determined. It may be assumed that the total amount of circulating protein in the blood remains constant, at any rate during short period observations. In this case the concentration of the serum proteins will give an indication of the degree of concentration or dilution of the plasma. The higher the percentage of serum proteins the greater the concentration of the plasma. The percentage of serum protein in the plasma was therefore used as a gauge of the degree of dehydration of the blood. This was determined by the Zeiss dipping refractometer for which only minute amounts of serum are required. In addition the blood chloride and non-protein nitrogen were estimated, the former because of the close association between chloride and water distribution in the body, the latter to afford some index as to the accumulation of waste products.

The composition of the blood in gastro-enteritis

The series of patients studied, all of whom were infants, can be divided into two groups:—(a) sixteen suffering from acute gastro-enteritis, and (b) fifteen marasmic infants with chronic diarrhoea. In each case the blood was first examined shortly after admission to hospital and prior to the administration of any parenteral fluid.

Serum proteins.—In group (a) eleven of the patients had high values varying between 8·46 gm. per cent. and 10·19 gm. per cent. and five had between 6·96 gm. per cent. and 7·85 gm. per cent. Marriott[1] and Webb[2] found that in acute infantile diarrhoea the serum protein is usually raised well above the values obtained in healthy infants. Cohen and others[3], on the other hand, found that in only four out of nine cases of acute infantile diarrhoea did the serum protein exceed 8 gm. per cent. The present results taken in conjunction with those of the last-named workers would indicate that in acute diarrhoeal conditions of infancy there is a tendency for the serum protein to be increased though this is not invariably the case. It would appear then that there is a tendency for the circulating plasma to lose water either into the tissues or into the gastro-intestinal tract.

In group (b) the serum protein was less than 8·0 gm. per cent. in all but one case, being as low as 4·92 gm. per cent. in one patient. These results are in accord with the findings of Courtney and Fales[4] and Marriott[5]. The last investigator also found that the percentage volume of red cells and percentage haemoglobin were reduced. This he suggested may be due either to the presence of too much water in the circulating blood or to disappearance of serum protein, red cells and haemoglobin. Thus while it is reasonable to assume in acute gastro-enteritis that a raised value for serum protein is indicative of loss of water the opposite conclusion cannot be drawn from a diminished value in chronic diarrhoeal conditions, since it may be an expression of many diverse factors such as passage of water to and from the tissues, previous malnutrition with its concomitant reduction of serum proteins, and excessive destruction of serum proteins.

Non-protein nitrogen.—Group (a). In ten patients the non-protein nitrogen varied between 47·1 and 97·4 mgm. per cent. and in three between 37·3 and 42·7 mgm. per cent. and in only one was it well within normal limits at 21·7 mgm. per cent. These results support the view of Cohen and others[3] that in most patients suffering from acute infantile diarrhoea there is a definite increase in the non-protein nitrogen of the blood. These authors also think that a close relationship exists between the level of the non-protein nitrogen and the degree of toxaemia. Hoag and Marples[6], however, obtained a definite increase in the non-protein nitrogen value only when the patient was moribund. The different results are probably to be attributed to differences in the degree of toxaemia and of dehydration in the various groups of patients.

The increase in non-protein nitrogen in acute infantile diarrhoea has been interpreted in various ways. Schloss[7] has suggested that it is the result of diminished renal action consequent on a depleted store of available fluid and Marriott's[5] view was that there was also an accelerated destruction of tissue protein. Probably both factors are present and the level of the non-protein nitrogen depends on whether or not sufficient fluid is available to carry away the products of tissue breakdown which almost certainly is increased.

Group (b). In all but four cases in which the non-protein nitrogen varied between 50·0 and 56·0 mgm. per cent. it was within normal limits. Nobécourt[8] found an increase in the urea content of the cerebro-spinal fluid in this type of case but Rohmer and others[9] obtained normal values. The smaller incidence of high non-protein nitrogen values in chronic diarrhoea than in the acute disease is probably due to the fact that in many cases the toxaemia is not so marked in chronic as in the acute condition. Furthermore the fact that the serum protein concentration is not increased in the patients with chronic diarrhoea indicates that loss of water from the blood is not a feature so that sufficient water is presumably available for the excretion of any excess of waste products that may be produced.

Chloride.—Group (a). Of the nine patients in whom the blood chloride was estimated only two had high values the other figures falling within normal limits. Similar observations have been reported by other workers[6, 10, 11, 12].

Group (b). In this group the values for blood chloride varied between 59·4 and 80·3 c.c. N/10 per cent., i.e., were either low or within normal limits. Courtney and Fales[1] have demonstrated that in athreptic infants the blood chloride is often low but may be normal or even high. The low values frequently found in chronic diarrhoea are probably the result of long continued malnutrition and loss of chloride in the faeces and vomitus, and the occasional high values may be an indication that the condition has taken on an acute phase with its attendant metabolic disturbance.

The blood chemistry pictures differ in acute gastro-enteritis and chronic diarrhoeal conditions. In the former the serum protein, non-protein nitrogen and chloride all tend to be high while in the latter low values are frequently obtained. Assuming that high serum protein indicates undue concentration of blood plasma, in other words a loss of water from the circulating blood it would appear from the tendency of blood chloride to be high that the water leaves the blood stream without its full quota of chloride. In chronic diarrhoea, on the other hand, when the plasma concentration is reduced as shown by the low values for serum protein the blood chloride tends to be on the low side so that here water enters the blood without its full quota of chloride. Accordingly, it would appear that in acute gastro-enteritis the primary need is for fluid to reduce the concentration of the blood and to act as a vehicle for the excretion of the accumulated waste products whereas in chronic diarrhoea the essential requirement is to enrich the diluted blood by a supply of protein and minerals.

The effect of parenteral fluid administration on the blood constituents

It has been demonstrated by many observers[3, 6, 13] that as the result of fluid administration to infants suffering from diarrhoea and vomiting, there results an improvement in their general condition; the kidneys begin to

secrete urine, the dehydration becomes less marked and the acidosis disappears. How these changes are brought about, however, is as yet imperfectly understood. There at present exists much confusion in the current ideas of the redistribution of water and chloride following the parenteral administration of fluid.

Greene and Rowntree[14] have shown that, when the volume of the fluid in the circulation of experimental animals is increased by forced water administration, much of the extra fluid introduced escapes from the circulation with great rapidity. In saline infusion experiments on dogs, Adolph, Gerbasi and Lefore[15] demonstrated similar rapid losses of fluid and also observed that chloride left the circulation even more rapidly than water. On the other hand, Davis[16] found in dogs that the vascular system did act as a fluid reservoir for he observed that the blood remained diluted for a period of five hours after infusion. The maximum blood dilution was usually not reached for a period of one hour, this initial dilution being immediately followed by concentration and later by further dilution.

The object of the present investigation was to determine the effects in infants of intravenous administration of fluid, given for therapeutic purposes, on the blood concentration as indicated by the level of the serum protein. For this purpose the serum protein was determined in infants before and at intervals after intravenous injection of saline-glucose solution. In all, three groups of patients were studied. These comprised (1) infants without any gastro-intestinal symptoms; (2) infants with acute gastro-enteritis; and (3) infants with chronic diarrhoea.

Group 1 —From the results in table 1, it will be seen that the non-protein nitrogen showed a slight fall over the three-hour period during which

TABLE 1

THE NON-PROTEIN NITROGEN OF THE BLOOD IN MGM. PER CENT. AFTER INTRAVENOUS SALINE

TYPE OF CASE	NAME	TIME AFTER INJECTION				
		BEFORE	½-HOUR	1 HOUR	2 HOURS	3 HOURS
Non-diarrhoeal	J. M.	38·2	37·8	37·8	37·3	35·5
	J. G.	30·7	30·9	27·6	25·2	25·5
	Average	34·5	34·3	32·7	31·2	30·5
Acute diarrhoea	A. J.	67·5	57·4	64·1	59·5	58·8
	R. M.	39·3	39·7	40·3	35·2	37·3
	Average	53·4	48·5	52·2	47·3	48·0
Chronic diarrhoea	W. A.	41·3	28·5	28·7	29·4	29·0
	A. M.	51·0	42·0	43·5	41·7	40·9
	P. H.	36·8	37·8	32·7	29·9	29·8
	C. D.	27·7	29·1	27·5	27·4	27·6
	A. H.	56·9	49·0	45·0	47·6	42·7
	Average	42·7	37·3	35·5	35·0	34·0

the examinations were continued. The total serum protein, however, showed rather characteristic and remarkable variations, more marked in some cases than in others (table 2). Thirty minutes after the injection,

TABLE 2

SERUM PROTEIN IN GM. PER CENT. AFTER INTRAVENOUS SALINE

TYPE OF CASE	NAME	TIME AFTER INJECTION				
		BEFORE	½ HOUR	1 HOUR	2 HOURS	3 HOURS
Non-diarrhoeal ...	J. M.	7·51	6·40	7·59	6·63	7·09
	J. G.	6·92	5·92	5·96	5·40	5·58
	J. N.	6·45	6·03	6·55	6·00	6·18
	C. S.	7·74	7·22	7·83	7·11	7·17
	Average	7·16	6·39	6·98	6·29	6·51
Acute diarrhoea ...	M. McL.	7·48	7·02	7·09	6·77	6·79
	I. M.	10·19	8·32	9·07	9·14	8·64
	V. F.	7·85	6·96	6·98	7·15	7·12
	A. J.	8·91	7·65	8·71	8·56	8·62
	H. McN.	9·39	7·96	8·26	8·91	8·69
	R. M.	7·26	6·14	6·49	6·85	6·36
	Average	8·52	7·34	7·77	7·90	7·69
Chronic diarrhoea ...	W. A.	7·78	6·55	6·85	6·83	7·96
	A. M.	6·70	6·27	6·72	6·29	6·42
	P. H.	6·09	4·92	5·29	5·60	5·38
	C. D.	4·92	4·54	4·84	4·50	4·48
	A. H.	6·49	5·79	5·64	5·36	5·53
	W. McF.	7·53	6·96	8·05	7·17	6·85
	M. McI.	6·68	6·34	7·39	6·88	6·72
	B. M.	6·29	5·65	5·81	5·05	5·58
	Average	6·56	5·88	6·32	5·96	6·12

there was a definite reduction of serum protein which most probably would have been still lower if specimens had been removed immediately after completing the saline injection. After the lapse of one hour the percentage of serum protein had risen in most cases to near, and in some cases above

the pre-infusion level. At two hours there was a fall which was more marked in some cases than in others, while at three hours a rise was again noted. It also appears probable that if specimens had been removed after the lapse of four to five hours, the serum proteins would have shown a reading very near to that of the pre-infusion level. These fluctuations in the serum proteins over such a short interval are probably to be explained by (1) alterations in the distribution of fluid between the circulation and the tissue spaces and (2) excretion of some fluid by the kidneys.

Miller and Pointdexter[17] have also demonstrated in dogs that the serum protein fell immediately after saline injections, commenced rising after fifteen minutes, but did not reach the pre-injection level at the end of one hour. Very similar findings are reported by Onozaki[18] who studied the serum protein values of rabbits for a period of seven hours after the intravenous injections of isotonic saline. He found that the serum protein concentration usually fell immediately after the injection, began rising at once and attained a value slightly lower than the pre-injection figure at the end of one hour, after which it again fell and did not quite reach the pre-injection value at the end of seven hours. He also mentions that similar changes were noted when the haemoglobin in rabbits was estimated after saline injections. It is evident therefore that the present results with infants closely resemble those obtained experimentally in animals.

Group 2. Acute infantile diarrhoea.—In this group the non-protein nitrogen was slightly reduced; in one of the two cases the reductions amounted to 8 mgm. per cent. (see table 1). Although the initial fall of serum protein immediately after the injection was just as marked as in the case of group 1 the rise at one hour was not so marked and the secondary fall if it did occur was sometimes delayed till the third hour (table 2). The variations of serum protein in these patients were thus less marked than in group 1, so that if it is accepted that the concentration of serum protein serves as an index of plasma volume concentration[19] it must be concluded that in patients with acute infantile diarrhoea the blood plasma remains diluted for a longer period than in cases in which dehydration is not present. This is in accord with the results obtained by Davis[16] who showed that in dogs suffering from the effects of dehydration the ability of the blood to hold both isotonic saline and glucose was greater than that found in normal animals.

The blood pressure according to Blalock, Beard and Theiss[20] and Adolph and Lefore[21] plays an important part in the redistribution of fluids during saline injections in animals. The latter investigators discovered that more fluid passed into the tissue spaces when the blood pressure was high than when it was low. It is possible that the slow passage of fluid from the circulation in cases of acute infantile diarrhoea may be due to a diminished blood pressure, although Hill[22] maintains that there is no diminution of the blood pressure in these infants. Attempts were made to estimate the blood pressure in several of the present series of patients but in only one was this successfully accomplished, and in this case the reading appeared to be low.

Group 3. Chronic infantile diarrhoea.—After saline injection the non-protein nitrogen in all cases except one showed a definite fall during the period of observation (see table 1). In the exceptional case the non-protein nitrogen, low at the beginning, remained at a constant level during the three-hourly period after saline injection. The variations of serum protein in this group were, however, not at all characteristic (see table 2). Some patients exhibited variations somewhat similar to those found in infants without gastro-intestinal symptoms (group 1), but with a much smaller range; others showed variations similar to those found in group 2.

The effect of calcium on the fate of fluid given intravenously

It has long been known that calcium is one of the substances which diminish the permeability of cells to water. A few studies were therefore made in an attempt to determine the effect on the serum of addition of calcium gluconate to the injected solution.

Group 1.—Administration of calcium to infants in whom no signs of dehydration were present caused little change in the fluctuation of serum protein after injection of saline (table 3).

TABLE 3

SERUM PROTEIN IN GM. PER CENT. AFTER INTRAVENOUS SALINE CONTAINING CALCIUM GLUCONATE

TYPE OF CASE	NAME	TIME AFTER INJECTION				
		BEFORE	½ HOUR	1 HOUR	2 HOURS	3 HOURS
Non-diarrhoeal	C. S.	7·35	6·47	6·63	6·34	6·68
	C. S.	7·35	6·51	6·79	6·70	6·42
	J. N.	7·13	6·42	6·79	6·18	6·29
	C. S.	7·65	7·39	7·44	7·11	7·24
	Average	7·37	6·45	6·91	6·58	6·66
Acute diarrhoea	B. I.	8·82	7·72	8·91	9·42	9·34
	M. B.	9·03	7·57	8·46	8·35	8·37
	Average	8·92	7·64	8·68	8·88	8·85
Chronic diarrhoea	C. B.	8·62	8·58	9·12	9·01	8·73
	B. M.	6·38	6·20	6·47	6·36	6·63
	Average	7·50	7·39	7·79	7·68	7·68

Groups 2 and 3.—Four infants, two with acute and two with chronic diarrhoeal conditions, were given calcium gluconate together with glucose and saline. Clinically the addition of calcium gluconate to the injection fluid did not appear to have any special effect on the patients' general condition. In both chronic cases the initial protein fall was minimal after injection, at one hour there was a rise to a value higher than the pre-injection level and then a gradual fall, so that three hours after injection the reading was still greater than in the first specimen removed (table 3).

In the two patients suffering from acute infantile diarrhoea, one showed a large and significant fall of serum protein as the result of the injection, followed by a steady rise until at two hours it reached a value greatly in excess of the protein level in the pre-injection specimen. At three hours the protein value showed a slight fall but still remained at a reading greater than the initial value of 8·82 gm. per cent. (table 3). Similar but not so marked findings were observed in the other case. It would thus appear that in infantile diarrhoea, when calcium gluconate has been given along with glucose and saline, the serum proteins exhibit alterations peculiar to the individual patient, but on the whole it would appear that in contrast to the findings in group 1 the presence of calcium in the fluid injected facilitates the transference of fluid from blood to tissues.

Discussion

The serum protein variations, occurring over a period of one to five hours after fluid injections in normal infants, appear to be similar to those described by Miller and others[17] in animals. During such a short space of time, the rapid and marked alteration of serum protein is in all probability due to alterations in the plasma volume. It would appear that, as the result of saline injection, there immediately occurs an increase of the plasma volume which gradually diminishes until at one hour, in most cases, it is smaller than the volume previous to the saline administration. This diminution in volume can only be explained by the fact that immediately after the injection the additional fluid is removed from the circulation. Most of it must pass to the tissue spaces and the water depots of the body as it would be impossible for the kidneys to deal with such a quantity of fluid within the short space of one hour. In several infants, it was observed that at one hour the serum protein value was higher than before the injection was given, indicating that more fluid had left the circulation than had been administered. It is thus evident that the circulation, in an attempt to remove the excess fluid, oversteps the mark and loses not only that introduced but also fluid previously in the blood stream. At two hours however, due to passage of fluid back from the tissues to the circulation, the serum protein shows a fall as compared with the value at one hour, but at three hours the plasma volume returns to the vicinity of its pre-injection level.

These findings indicate that, as the result of fluid injections in normal infants, a to-and-fro movement of fluid takes place between the blood plasma

and the water depots of the body until after the lapse of three to four hours, the normal water content of the plasma is reached and maintained. This is probably due to the establishment of increased renal activity and removal of surplus fluid.

The mechanism regulating the passage of fluid from one tissue to another is imperfectly understood, but the finding of Blalock and others[20] that, in dogs with a lowered blood pressure, fluid passed much more slowly from the circulation into the tissue spaces than in dogs with a normal blood pressure, would seem to indicate the importance of blood pressure as one of the regulating factors. There is also no doubt, that osmotic action and the capacity of the water depots and tissue spaces of the body to absorb fluid, take a part in initiating these movements.

In patients suffering from acute infantile diarrhoea there also occurs a definite increase in the plasma volume as the result of saline and glucose injections—shown by the fall of serum protein at the half hour period after injection—but the plasma remains diluted for longer than occurs in normal infants. It is also evident that the amount of fluid passed either in the tissues during the first hour or back into circulation during the second hour, is never as great as occurs in patients without gastro-intestinal disturbances. The slower and smaller fluid alterations between the circulation and the tissues of acute diarrhoea are probably to be attributed to (a) a lowered blood pressure[20, 21]; (b) increased affinity of the circulation for fluid[16]; (c) diminished affinity to the tissues for fluid; or (d) some other abnormality such as alteration of osmotic pressure. The increased concentration of blood constituents which is known to occur in most cases of acute infantile diarrhoea[1] might readily result in an increased affinity of the circulating blood for the administered fluid.

In chronic infantile diarrhoea it would appear that in some patients the normal movements of fluid between the circulation and the tissues is also upset, but to a much less marked extent than occurs in acute cases. In others, however, the movements appear even more exaggerated than those found in infants without diarrhoea.

Addition of calcium gluconate to the saline and glucose solution had in infants without diarrhoea (group 1) little effect on the fluctuations of fluid between the tissues and the blood plasma. In three of the four acute and chronic diarrhoea cases the use of the calcium gluconate seemed to accelerate the passage of the injected fluid from the circulation to the tissue spaces. It is possible that this might be the result of the well-known action of calcium in increasing the efficiency of the heart's action. The presence of calcium in the injected fluid, therefore, may be of advantage in promoting the transfer of fluid to the tissue spaces and preventing its over-rapid return to the circulating blood. It is also possible that in this way more fluid could be administered without causing embarrassment to the circulation.

Summary

The serum protein and non-protein nitrogen and chloride of whole blood were estimated in cases of acute gastro-enteritis and chronic diarrhoea. In the former the serum protein, non-protein nitrogen and chloride all tended to be high while in the latter low values for protein and chloride were frequently obtained and the non-protein nitrogen generally fell within normal limits.

The significance of these findings is discussed and it is suggested that in acute gastro-enteritis there is a loss of water from the circulating blood and that the water leaves the blood stream without its full quota of chlorine. In chronic diarrhoea it would appear that water enters the blood without its full quota of chlorine.

As a result of saline and glucose injections characteristic alterations occur in the serum protein of normal infants. In infants with acute gastro-enteritis these alterations are much less marked and it is concluded that the blood plasma remains diluted for much longer than in the infant without dehydration.

The results of adding calcium gluconate to the injected fluid suggest that in infantile diarrhoea calcium gluconate may be of some benefit in accelerating the movement of fluid from the circulation to the tissue spaces.

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III.—CHANGES IN WATER AND CHLORIDE CONTENT OF THE TISSUES IN INFANTILE DIARRHOEA AND OTHER CONDITIONS

Chloride plays an important part in the general metabolism especially in the regulation of the water exchanges of the body and the neutrality of the tissue fluids, matters which are of outstanding importance in the early months of life. The chloride is replenished by food and is excreted mainly by the urine and sweat. Although normally only small amounts are lost by the bowel, in diarrhoea the faeces may contain as much as 15 gm. NaCl per litre[1]. Excessive diuresis, vomiting or profuse sweating may reduce to a dangerous degree the chloride of the body and with it the water reserves of the organism. Excessive loss of chloride through one channel causes a diminished excretion from others; thus infants suffering from pyloric stenosis show a decreased output of urinary chloride owing to excessive loss in the vomitus.

Water is essential for the biochemical changes which are constantly taking place in animal life; it acts as a medium for the cell nutrition and also as the vehicle for the transfer of waste products resulting from growth and metabolism. According to Underhill and Fisk[2] the amount of water that can be mobilized probably depends on the quantity of available ' free ' or interstitial water present in the tissues. This ' free ' water is presumably chemically uncombined and therefore capable of being shifted about via the blood stream. In contra-distinction to this, the ' bound ' or intra-cellular water probably forms an integral part of protoplasm. Its loss would immediately lead to tissue death. From their experimental work on adults Wiley and Wiley[3] believe that the ' bound ' water is drawn upon when the organism is in dire need of fluid.

In diseases such as cholera, where quantities of chloride are lost from the body there also occurs a corresponding loss of water, so that dehydration soon appears. Water as well as chloride is essential in the treatment of this type of case for the tissues and body fluids to regain their normal composition; not till then will tissue function be restored and the excretion of waste products recommence.

It is obvious that as the metabolic processes in the tissues are constantly in a state of flux, there cannot be a definite ' normal ' chloride or water content for any of them. The process of dying almost certainly alters them unless it is instantaneous, so that the nearest approach to determining a normal average range of chloride and water concentration can only be obtained by analysis of tissues from cases of sudden death, and such cases are rare in infancy.

A careful search of the literature revealed the paucity of data of this nature in both adults and children, but more particularly in the latter. The average tissue chloride values for infants have been estimated by Morris

and Graham[4] in a few cases. In adults Magnus-Levy[5] has estimated the values for the chloride in tissues obtained from a case of suicide, while Ballif and Gherscovici[6] obtained their figures from three cases of accidental death. Müller and Quincke[7] have also estimated the average chloride content of tissues obtained from five adults killed in accidents. The findings of these four authors may profitably be compared, and are set down for this purpose in table 1. It will be at once observed that the values vary widely

TABLE 1

AVERAGE VALUES (C.C. N/10 PER CENT.) FOR TISSUE CHLORIDE IN ADULTS AND CHILDREN

TYPE OF CASE	AUTHORS	KIDNEY	MUSCLE	HEART	LUNG	LIVER	BRAIN
Adult— Accidental Death	Magnus-Levy[5] ...	59·3	17·4	34·7	63·5	42·3	36·8
	Ballif and Gherscovici[6]	—	21·2	—	—	—	44·5
	Müller and Quincke[7]	39·0	21·3	—	50·0	33·3	—
Infants—	Graham and Morris[4] ...	42·1	43·2	37·7	52·4	36·5	48·9

although all the adult material used was obtained from the same type of case—accidental and sudden death. Ballif and Gherscovici[6] in another series of sixty patients, dying from various causes found great variations in the different tissues, some showing a chloropenia, others a chloropexia, but they mention that brain tissue appears to be the tissue of election for fixation of chloride.

Various diseases apparently lead either to a retention or a loss of chloride from the tissues. Thus von Moraczewski[8], Hutchison[9], and others[10] have shown that in adult cases of pneumonia there occurs an increased retention of chloride, not in any one particular tissue, but in the body tissues as a whole. In patients suffering from obstructive vomiting, due to high intestinal obstruction Brown, Eustermann and others[11, 12] have demonstrated a marked chloropenia of most tissues. Morris and Graham[4] have similarly demonstrated a tissue chloropenia in infants with pyloric stenosis who had not previously received saline treatment.

The average water content of a number of the more important tissues in adult subjects has been estimated by various observers and it is interesting to note that the average values for each of these tissues show much more uniformity than do those for chloride (table 2). In infants, however,

TABLE 2

WATER CONTENT OF TISSUES (ADULT) AS PERCENTAGE OF TOTAL WEIGHT

AUTHOR	KIDNEY	MUSCLE	HEART	LUNG	LIVER	BRAIN
Magnus-Levy[5]	75·6	72·2	74·8	80·0	60·6	77·9
Hutchison[9]	—	75·0	—	79·4	75·6	—
Blum & Brown[23]	79·7	73·4	—	—	67·7	82·0 (grey) 70·0 (white)
Engels[16]	82·7	75·6	79·2	78·9	68·3	74·8

McQuarrie[13] found that the percentage of water content of the body varies inversely with age. It would thus seem that the water requirement in infancy is greater than in adult life which probably explains the serious danger of any sudden and severe dehydration. According to this author, when water has been given in excess, the amount of fluid not excreted by the kidneys is probably stored in the interstitial spaces, which serve as adjustable reservoirs according to the needs of the individual.

Present investigation

The aim of the present investigation was to determine if there are any alterations in the chloride and water content of the tissues after death from various diseases, but particularly in infants dying from diarrhoea for, as is known, in these patients large amounts of fluid are lost by the severe vomiting and the frequent loose stools. Incidentally the opportunity was taken as occasion arose to determine if the chloride and water contents of the tissues were significantly affected by parenteral administration of saline during the three days prior to death.

The material used in these investigations was a series of sixty-seven infants dying from various diseases. The tissues were removed at autopsy in quantities sufficient for the estimation of both the chloride and water content. The following list shows the diseases causing death and the numbers included under each disease.

1.	Miscellaneous control group (meningitis, cerebral haemorrhage, pyuria and neonatal anaemia)	24 cases
2.	Infantile diarrhoea	16 ,,
3.	Infantile diarrhoea with broncho-pneumonia	10 ,,
4.	Broncho-pneumonia	11 ,,
5.	Peritonitis	3 ,,
6.	Intestinal obstruction (pyloric stenosis and atresia of bowel) ...	3 ,,

They formed a consecutive series of post-mortem examinations performed in the Pathological Department of the Royal Hospital for Sick Children, Glasgow.

Immediately after the post-mortem examinations, duplicate specimens averaging 5 gm. were placed in previously weighed and dried containers. The exact weight of each specimen was then noted and the chloride content determined on one specimen by means of the silver nitrate method of van Slyke[14]; the results were expressed in c.c. N/10 Cl per cent. The second specimen was placed in a special oven maintained at constant temperature, until the weight remained constant. From the initial and final weights the percentage water content was calculated.

Tissue chloride.—Since there are no reliable data as to the normal values for tissue chloride in infants, the results of analysis of tissues obtained from a group of patients who died from various causes which appeared

unlikely to affect chloride metabolism, have been used to indicate the normal chloride content (table 3). Even in this control group there were marked

TABLE 3

AVERAGE VALUES (C.C. N/10 PER CENT.) FOR TISSUE CHLORIDE IN VARIOUS DISEASES

DISEASE	TREATMENT	MUSCLE	LIVER	HEART	KIDNEY	BRAIN	LUNG
Miscellaneous control cases	No saline	38·0	40·6	43·4	47·7	52·3	61·4
	Saline	51·7	38·6	37·8	47·5	43·1	61·0
Infantile diarrhoea	No saline	35·9	39·9	37·5	40·5	51·8	57·5
	Saline	62·3	58·5	53·7	62·1	60·2	70·0
Diarrhoea with pneumonia	No saline	40·5	50·7	42·0	50·5	46·9	61·3
	Saline	62·9	53·0	43·3	52·2	51·3	60·7
Bronchopneumonia	No saline	43·5	43·5	44·5	49·2	43·2	67·9
	Saline	59·1	50·7	49·0	51·2	50·5	69·3
Peritonitis	No saline	43·6	46·0	38·6	39·6	45·9	59·0
	Saline	55·0	62·6	42·5	61·7	—	79·1
Intestinal obstruction	No saline	42·1	44·6	37·9	46·1	—	47·0

variations in the individual chloride values in different subjects. A similar variation has been commented upon by Ballif and Gherscovici[6] in adult material. Unfortunately these results are open to the criticism that alterations of the distribution of tissue chloride may have taken place during the process of dying, so that the findings may not give a true expression of the state of the tissues in health.

In the present series age did not appear to have any influence on the chloride value of any of the tissues, nor did the duration of illness.

The average values are given in this paper but in view of the variation in the ' normal ' group it should be emphasized at the outset that only great departures from the ' normal ' average can be considered significant. Examination of the values obtained for chloride (table 3) shows that the lowest content occurs in muscle (skeletal) increasing progressively in liver, cardiac muscle, kidney and brain to a maximum in lung. Schnohr[15] also found the lowest chloride content in muscle with a progressive rise through brain, spleen, kidney and skin to a maximum in lung and, states that these values have been confirmed in man and animals by other investigators.

In infantile diarrhoea and vomiting, when no saline had been administered during life, the tissues of muscle, heart, kidney and lung contained practically the same amounts of chloride as those of the miscellaneous control group. It would thus appear that in patients with infantile diarrhoea, only slight and insignificant losses of chloride occurred from the fixed tissues; this is in contrast to the low chloride values found in congenital stenosis of the pylorus. In the group of patients with bronchopneumonia the chloride content was slightly higher than in the control series in all the tissues except the brain. When infantile diarrhoea and bronchopneumonia occurred together, however, only the liver chloride was increased. In two patients dying from peritonitis a diminished chloride content was noted in the brain, heart and kidney tissue, the other organs exhibiting values either above or similar to those of the control group. In those patients dying as the result of bowel obstruction the average chloride values for the tissues were found to be low, but did not reach the low levels found by Graham and Morris[4] in pyloric stenosis.

Average water content—various diseases

With regard to the average water content of the tissues of untreated cases of the miscellaneous control group, it will be observed (table 4) that

TABLE 4

AVERAGE WATER CONTENT (GM. PER CENT.) OF TISSUES IN VARIOUS DISEASES

DISEASE	TREATMENT	MUSCLE	LIVER	HEART	KIDNEY	BRAIN	LUNG
Miscellaneous control group	No saline	76·2	76·6	81·1	80·8	87·2	80·8
	Saline	77·9	74·5	83·1	82·2	87·0	83·3
Infantile diarrhoea ...	No saline	75·1	73·8	80·3	80·1	86·4	80·3
	Saline	78·7	76·5	81·5	82·0	87·4	80·7
Diarrhoea with pneumonia	No saline	75·4	77·7	81·7	80·3	85·2	80·5
	Saline	78·9	78·2	82·2	81·8	86·6	81·2
Bronchopneumonia ...	No saline	73·9	74·9	79·7	81·5	85·5	81·6
	Saline	72·6	75·7	80·8	80·8	—	80·9
Peritonitis	No saline	76·9	74·9	82·4	80·8	87·5	79·6
	Saline	80·0	78·2	81·4	82·2	—	87·3

the values varied between 76·2 per cent. in muscle, and 87·2 per cent. in brain. These values are on the whole greater than the water content of adult tissues.

From examination of table 4 it will be noted that the average water content is fairly constant, no disease showing a significant departure from normal. Even in the diarrhoea group the average values are only slightly lower than for similar tissues in the untreated control group. It must be pointed out, however, that this slight reduction in percentage water content may conceal a considerable loss of fluid. Thus, as the following calculation shows, it is possible that as much as one kgm. of water may be lost by an infant weighing 5 kgm. with only a 5 per cent. reduction in the water content of the tissues.

	Total weight in gm.	Weight of water in gm.	Weight of solids in gm.	Per cent. water content
Prior to loss of water ...	5,000	4,000	1,000	80
After loss of 1 kgm. of water	4,000	3,000	1,000	75

No relationship was noted between the water content of the tissues and the duration of the illness or the terminal temperature.

Effect of administration of saline

(a) Chloride content of the tissues.—A consideration of those of the miscellaneous control patients to whom saline had been given within three days of death, shows that a marked increase of tissue chloride occurred only in muscle tissue, the other tissues exhibiting only slight variations (see table 3). This differs from the findings of Schnohr[15] who demonstrated an increased retention of chloride in the brain of animals receiving saline before death.

As a result of saline administration to infants with diarrhoea a marked increase of chloride occurred in all tissues but this was specially marked in muscle, liver, kidney (see table 3). Morris and Graham[4] have also shown that in infants with pyloric stenosis to whom saline had been administered before death, there occurred a marked increase in the chloride content of all tissues. In the present series the fixation of chloride following injection of saline was more marked in patients dying from gastro-enteritis and peritonitis than in those dying from other diseases, although the increase of chloride was apparent in all the groups. In patients dying from the effects of infantile diarrhoea, the increase of chloride after parenteral administration of saline was most striking in the first trimester of life (table 5).

TABLE 5

Average values (c.c. N/10 per cent.) for tissue chloride in infantile diarrhoea at various ages

Age in months	Muscle	Liver	Heart	Kidney	Brain	Lung
0–1	69·8	65·8	52·6	68·4	62·6	74·5
1–3	68·2	63·4	56·2	63·2	62·2	69·1
3–6	57·9	48·4	49·7	54·7	56·5	69·5
Over 6	48·2	40·1	40·8	50·8	—	58·8

(b) **Water content of the tissues.**—The effect of administration of fluid was to increase slightly the average water content of most of tissues. In some, particularly muscle, this increase is well shown (see table 4). Engels[16] has also demonstrated that in dogs, following intravenous injection of isotonic saline solution, there occurred an increase of water in all tissues, but that two-thirds of the fluid retained was stored in muscle tissue and one-sixth in the skin. The present results would tend to confirm his findings. Generally, the younger the subject the more marked was the increase in the water content of the tissue.

Relationship of chloride and water content to state of nutrition

In order to determine the relationship between the state of nutrition and the chloride and water contents, the series was divided into three groups, (a) cases under 50 per cent. of expected weight, (b) those between 50 and 70 per cent. and (c) those over 70 per cent. Generally but not invariably the more undernourished the infant the greater was the percentage content of water and chloride of the tissues whether saline had been given or not.

In the infantile diarrhoea group particularly, the tissues of the most malnourished infants exhibited the highest chloride and water content (tables 6 and 7). It is possible that this finding can be explained by a loss

TABLE 6

AVERAGE VALUES (C.C. N/10 PER CENT.) FOR TISSUE CHLORIDE IN INFANTILE DIARRHOEA AT VARIOUS STATES OF NUTRITION

PERCENTAGE OF EXP. WEIGHT	MUSCLE	LIVER	HEART	KIDNEY	BRAIN	LUNG
Under 50 ...	66·0	66·1	52·7	71·4	—	76·1
50-70	65·6	59·2	53·4	61·8	64·2	71·1
70-100...	54·6	55·3	54·4	60·3	54·1	65·3

TABLE 7

AVERAGE VALUES FOR WATER CONTENT (GM. PER CENT.) OF TISSUES IN INFANTILE DIARRHOEA AT VARIOUS STATES OF NUTRITION

PERCENTAGE OF EXP. WEIGHT	MUSCLE	LIVER	HEART	KIDNEY	BRAIN	LUNG
Under 50	82·0	80·0	83·8	84·3	—	86·3
50-70	79·6	78·6	82·0	82·3	87·9	80·9
70-100	76·9	74·4	80·0	80·9	86·7	79·4

of fat or a breakdown of tissue cells with the liberation of bound water. It appears rather unlikely that the cells themselves can be broken down without loss of both chloride and water, although it must be admitted that

cell shrinkage may take place and with it an increased fixation of chloride owing to tissue damage. This view, however, does not explain the increase in the water content of the tissues. An increase of chloride and water in the liver tissue of athreptic infants has been described by Franke and Stolte[17], while Ohlmuller[18] also demonstrated that the water content of the organs of athreptic infants is greater than those of normal infants. Miller[19] mentions that fat contains only about 10 per cent. water, so that in patients with severe fat loss a proportionately increased water content will result. It seems probable that loss of fat is the main factor in the increased percentage content of chloride and water in the tissues of the severely undernourished patients. If this is the case it is probable that the high percentage of water and chloride found by us in undernourished infants are due not to accumulation of water and chloride but to loss of fat.

Discussion

The chloride content of the tissues in the various disease groups does not show significant variations from that found in the control series. The values tend to be low in infantile diarrhoea and peritonitis and high in bronchopneumonia, but there is certainly no definite evidence that there is a tissue chloropenia in infants with diarrhoea and vomiting as suggested by Seckel[20] and Mellinghoff[21]. The values reported here for patients with infantile diarrhoea and vomiting are much higher than those recorded by Morris and Graham[4] for congenital pyloric stenosis. This, of course, might be due either to the much greater severity of vomiting in pyloric stenosis or to some difference in the metabolic disturbance in these two conditions. At any rate it can be concluded that in infantile diarrhoea the loss of chloride from the tissues is not as great as has been supposed.

As the result of saline administration, there occurred a marked increase in the chloride content of all tissues of the infantile diarrhoea and peritonitis groups. The other groups, with the exception of the control series also showed this increase but to a very much less marked extent. This definite chloride increase in the infantile diarrhoea group might be due to (a) a chloride vacuum in the fixed tissue, i.e., chloropenia, (b) a diminution in the power of the kidneys to excrete chloride owing to an insufficiency of water for transport purposes, or (c) deposit of chloride as the result of tissue damage[22]. It has been demonstrated, however, that in contradistinction to what occurs in pyloric stenosis, no evidence of a definite chloropenia exists in these patients with infantile diarrhoea, so that it seems more likely that the increased chloride fixation after saline is due either to a diminution in the power of the kidneys to excrete chloride or to accumulation of chloride as the result of tissue damage. The view that renal dysfunction is the main cause is supported both by the fact that anuria was present in many of these patients and that there was retention of nitrogen waste products as evidenced by the high non-protein nitrogen of the blood.

Summary

1. The chloride and water content of the tissues of infants is greater than that of adults.

2. No definite loss of chloride or water from the tissues of patients dying from infantile diarrhoea and vomiting can be demonstrated.

3. In both infantile diarrhoea and peritonitis, as the result of saline administration, a marked fixation of both chloride and water occurs in the tissues. Muscle appears to be an important depot for this storage.

4. The younger the infant the greater the capacity to fix chloride and water as the result of saline administration.

5. No definite relationship between the chloride and water content and the duration of illness, or the terminal temperature is apparent.

6. Patients with the most severe malnutrition often exhibit high chloride and water contents and also greater retention of these substances after saline administration.

7. It is suggested that increased fixation of chloride in tissues after injections of saline is due to renal insufficiency.

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STUDIES IN ANAEMIA OF INFANCY AND CHILDHOOD

BY

LEONARD G. PARSONS, M.D., F.R.C.P., EVELYN M. HICKMANS, PH.D., M.Sc., and ETHEL FINCH, M.Sc.

(From the Children's Hospital and the Department of Diseases of Children of the University of Birmingham.)

Part XI.—The effect of iron deficient diets on the size of the red blood cells in rats and in the production of microcytic hypochromic anaemia in their offspring; a contribution to the study of congenital iron-deficiency anaemia in the human infant

The studies of anaemia in infants and young children which have been carried out by our colleagues and ourselves (Parsons et al.[11, 12, 13, 14]) have shown that the maturation of the red cell is a somewhat more complicated process than that suggested by Witts. For instance, vitamin C and thyroxin are concerned not only with the maturation of the normoblast to the erythrocyte but also act throughout the whole range of erythropoiesis. This statement is based upon the fact that when anaemia occurs as a result of a deficiency of either of these two factors, it is never of the hypochromic and microcytic type, but usually orthochromic and normocytic, although sometimes a macrocytic anaemia may result. Further a true microcytic anaemia is essentially due to a deficient supply of iron to the bone marrow, although it may occur in the absence of certain substances containing the pyrrol ring, possibly also of calcium, and, at any rate experimentally, in the absence of copper and perhaps some other metals which act as mobilizers or catalysts of iron.

In the course of these investigations, Helen Mackay's view[8] that nutritional anaemia is frequent in infancy has been confirmed; it has also been shown that this form of anaemia may occur as the result of deficiency of dietary substances containing the pyrrol ring, and that it is accompanied by a microcytosis which gives place to a normocytosis when the anaemia is cured by the supply of the missing factors, e.g., iron, copper, pyrrol. Moreover, evidence has been obtained of the existence of a congenital nutritional anaemia which, it is believed, is due to inadequate maternal diet during pregnancy. The experiments described in this present paper were undertaken to test and extend these views on microcytosis and congenital anaemia by means of controlled animal experiments.

Variations in the number and size of red cells of the rat from birth to maturity

Nutritional anaemia in the rat exhibits the same features as regards haemoglobin values, number of red blood cells, and response to iron therapy as the nutritional anaemia of infancy, and indeed also as that of idiopathic hypochromic anaemia of adults. In the study of experimental anaemia, attention has been almost entirely focussed on haemoglobin estimations and to a lesser extent on red cell counts. Moreover the existence of a microcytosis such as occurs in the iron deficiency anaemia of human infants and adults has only been demonstrated by one observer (Foster[5]) who made use of the haematocrit method. It was therefore determined to plan a series of experiments to obtain accurate information, by means of Price Jones' curves, concerning the size of the red cells of rats fed on a diet deficient in iron and of the progeny of such rats; also to follow the changes in size, if any, brought about by the addition of adequate amounts of iron to their diet. In order to assess the importance of any changes found in these rats, it was necessary in the first place to obtain information about any variations that occurred in the number and size of red cells in the normal rat from birth to maturity.

Sure, Kik, and Walker[17] found that there was a continuous increase in the number of red cells from 2·8 millions at birth to 6·0 millions or over at twenty-nine days, whereas according to Wills and Mehta[20] the red cells diminish in number until the tenth day of life and then rise rapidly. Smith[16] who made observations on groups of five rats at the following age periods: two days before term, one, two, three, four, five, six, seven, ten, thirteen, nineteen, twenty-three and seventy-three days, and in adult life, was, however, able to confirm and extend the findings of Sure, Kik and Walker, and showed that there was a steady rise in the number of red cells from 2·1 millions at birth to 8 millions in adult life.

The present investigation confirms the statement that a continuous increase in the number of red cells takes place from birth to maturity. For the purpose, normal stock rats (both albino and piebald) were used and counts were made on five rats in each group at ages of one day, one, two, three, four, six, eight, and twelve weeks, and the count was found to increase from 2·8 millions at birth to 7·8 millions at three months of age (see table 1). This striking increase in the number of cells as the animal matures is a fact for which at present no explanation can be offered, and is a phenomenon which is quite unlike anything that occurs in the human infant; in fact, it is the exact opposite of what usually obtains. It is generally accepted that there is a fairly rapid drop in the number of red cells in the first few days of the new-born child's life. Guest[6] has, however, found that sometimes in the first few days of life there is an actual increase in the number of cells and our colleague, Dr. Margaret Cleland, who is making observations on the blood of new-born children, finds that an increase in the red cell count of something like half a million does sometimes occur in the first two or three days of life. Such an increase is, however, small when compared with the rat and is probably due to dehydration. In this respect the young rat and the infant show a marked difference, but on the other hand the rat shows a continuous fall in the amount of haemoglobin until the fourth week of life which is strictly comparable with the physiological anaemia of infancy.

Wills and Mehta in the paper already mentioned recorded some measurements of the size of the red cells using a simple halometer method; the only measurements made by the Price Jones' technique are contained in Smith's paper. She proved that during growth there was a progressive reduction in the size of the cell from a mean diameter of 9·91μ in the foetus two days before term to 6·08μ in the adult rat.

The size of the red cells in rats in the present investigation have been measured by means of Price Jones' curves and a similar result obtained, the average mean diameter ranging from 8·79μ at birth to 6·19μ at three months. The full details of the red cell counts, the size of the red cells, the number of reticulocytes and the amount of haemoglobin are given in table 1,

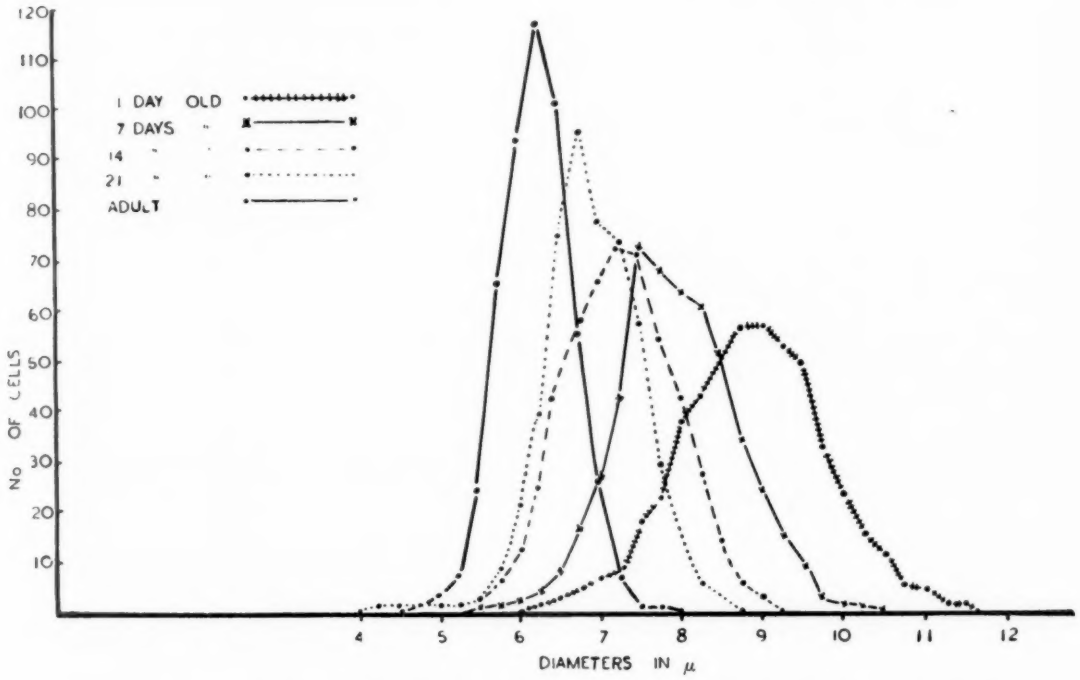

FIG. 1.—Composite curves for five rats showing the alteration in the mean diameters of the red cells from birth to maturity.

and in figure 1 are shown a series of composite curves of the diameters of the cells from birth to three months.

This gradual diminution in the size of the red cell also occurs in the human infant, but to a much less degree; thus van Creveld[2] has shown that there is a megalocytosis at birth, the mean diameter being 8·0μ, but that the cell diameter diminshes after the neonatal period and is 7·72μ in the eighth week of life. It is clearly important, therefore, that in any study of the possible alteration in the size of the red cells as the result of diet, this physiological change in the size of the cell must be borne in mind, and for this reason the Price Jones' curves of the red cells of anaemic rats have been checked by parallel measurements of the red cells of normal stock animals of the same age. Similar controls have also been used for all haematological observations.

TABLE I.

Hb. per cent., R.B.C., reticulocytes and red cell diameter measurements of young rats
1. born from parents receiving stock diet and continued on stock diet.
2. ,, ,, ,, ,, iron-deficient diet and continued on (A) iron-deficient solid diet or (B) milk only.

	Parents receiving stock diet					Parents receiving iron deficient diet				
Age of litter	Hb.	R.B.C. in millions	Retics.	Mean diameter	C.I.	Hb.	R.B.C. in millions	Retics.	Mean diameter	C.I.
1 day	86	2·810	56	8 79	2·44	80	2 569	57	7·93	2·5
1 week	81	3·200	39	7·91	2·02	47	3·290	19	7·6	1·14
2 weeks	73	4·150	25	7·73	1·41	30	3·16	40	6·4	0·76
3 weeks	67	4 490	17	6·95	1·19	24	4·29	27	6·00	0·45
		Continued on stock diet					Continued on iron deficient diet			
4 weeks	89	6·370	14	6·69	1·12	39	4·7	20	5·66	0·67
6 weeks	92	7·700	14	6·32	0·96	48	6·39	13·9	5·55	0·61
8 weeks	93	7·440	4·7	6·24	1·00	80	11·2	Few	5·67	0·57
12 weeks	93	7·760	2·6	6·19	0·96	105	11·3	Few	5·67	0·74
		Continued on milk only from 21 days					Continued on milk only from 21 days			
8 weeks	—	—	—	—	—	18	5·0	13·1	5·41	0·28
12 weeks	22	4·1	8·9	5·7	—	16	3·85	12·7	5·40	0·33

C.I. is worked out for Normal Hb. adult rat = 100 per cent.
,, Reds ,, ,, = 8,000,000.

Effect of a low iron diet on the number and size of red cells of rats and of their progeny

In a previous paper (Parsons and Hickmans[12]) it has been shown that nutritional anaemia in rats could be prevented by the addition of dried yeast to a milk diet after the end of a normal period of lactation, but that the offspring of rats so fed showed a profound anaemia even during the lactation period. Although such a diet does not contain an adequate amount of iron it is not ideal for the purpose of these experiments because the amount of milk makes the diet so bulky that it is impossible for pregnant rats to take enough food to keep up their weight. A solid diet was therefore constructed which, although low in iron, is not, according to present knowledge, deficient in other respects. This diet consists of:—

Rice starch	60 per cent.
Casein	20 ,, ,,
Palm kernel oil	10 ,, ,,
McCollum's salt mixture (omitting the iron compound)	5 ,, ,,
Yestamin	5 ,, ,,

Fifteen grammes of this mixture made into a thick paste with cows milk and supplemented by two drops of cod-liver oil and two drops of wheat germ oil were given to each adult rat daily. Stock rats fed on this diet from the time of weaning (at about three weeks of age) to three months of age show practically normal growth and do not appear pale or anaemic, their haemoglobin being approximately 100 per cent. (16 gm.); indeed, in only one instance has a percentage as low as 70 been found, this being in a pregnant rat. The red cells, however, show a relatively large increase in number, the count usually ranging from 9 millions to 11 millions as compared with a normal count of 7 to 8 millions per c.mm.; moreover the red cells are smaller than normal, the diameter verying from 5·5μ to 5·8μ as compared with the normal diameter of 6·19μ.

The result of this diet is, therefore, to produce a microcytosis and a lowered colour index, although the haemoglobin percentage remains unchanged. Moreover, the litters produced by these rats are particularly interesting. At birth their haemoglobin and red cell count are generally only slightly sub-normal, but on comparatively rare occasions haemoglobin readings as low as 10 per cent. have been observed. During the lactation period, however, the haemoglobin is rapidly reduced to a level below that found in the physiological anaemia of early life, often falling as low as 10 per cent.; further, the number of red cells rises less rapidly than in the normal rat. The red cells at birth are smaller than normal and they steadily diminish in size during the first three weeks of life, as do the cells of the normal rat. If, when weaned, these young rats are given the same iron-deficient diet as their parents the haemoglobin rises rapidly and the red cells increase up to 11 millions; nevertheless the mean diameter continues to be small, viz., 5·7μ as compared with 6·12μ for the stock animals. If instead of this special diet they are fed only on milk their haemoglobin percentage continues to fall and the red cells diminish to less than 4 millions,

and their diameter falls to about 5·4μ. A similar, although not so marked, diminution in haemoglobin and in the number and size of the red cells occurs when rats born of stock parents are given milk only for the first three months of life. These results are set out in detail in table 1. In fig. 2 the variations are compared by means of graphs with those of rats on stock diet, and in fig. 3, Price Jones' curves of the size of the red cell at various ages are depicted, together with the corresponding curves for rats of the same age on stock diet.

From these results it is obvious that a diet has been devised which, although low in iron, contains just sufficient iron to enable the adult rat to maintain a normal haemoglobin level, but insufficient to allow the normal complete maturation of the red cell to take place. On such a diet many

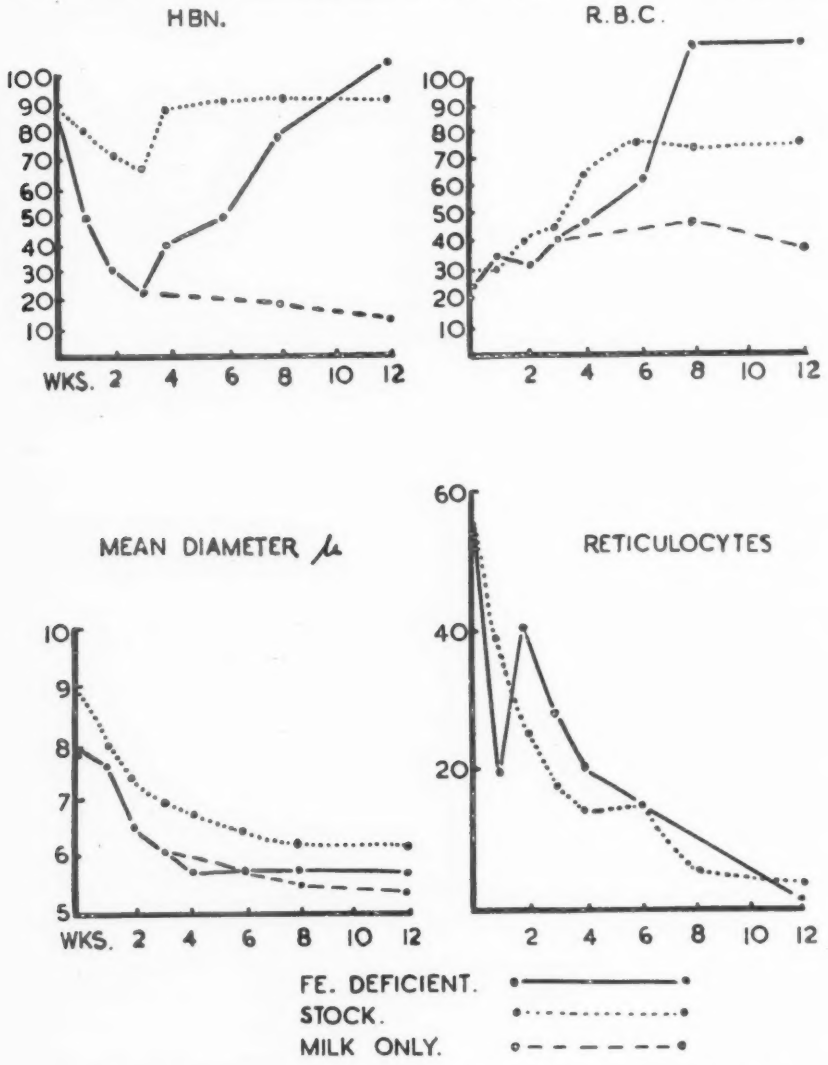

FIG. 2.—Showing the Hb., red blood cell count, reticulocytes and mean diameters of red cells of rats:
1. Born of parents fed on stock diet
2. ,, ,, ,, ,, ,, iron-deficient diet
and continued from lactation on similar diets or milk only.

of the red cells are smaller than normal but the haemoglobin is kept at the normal level by the development of a polycythaemia. We believe that in all iron deficiency anaemias the bone marrow hypertrophies in an attempt to produce large numbers of small envelopes (microcytes) to hold

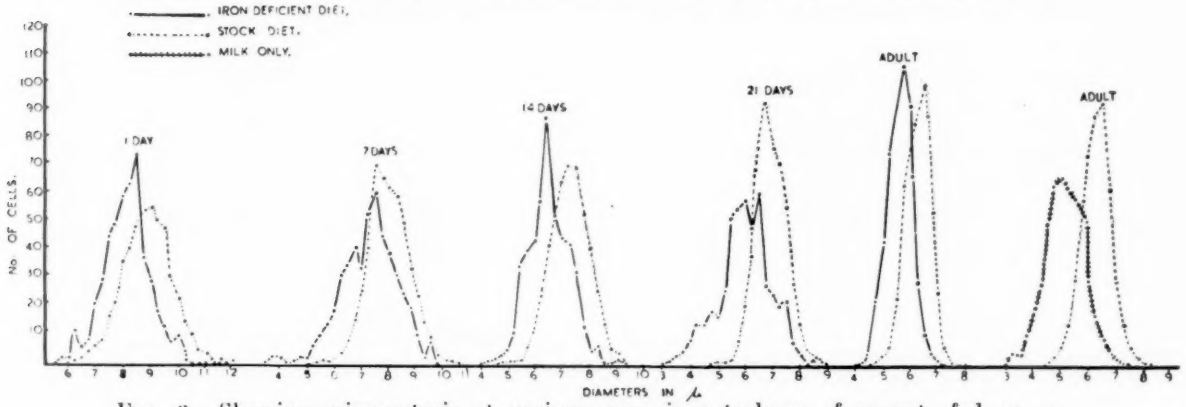

FIG. 3.—Showing microcytosis at various ages in rats born of parents fed on an iron deficient diet and continued on the same iron deficient diet or on milk only.

the available haemoglobin and thus to offer the largest possible surface area of haemoglobin for gaseous exchange. Although it may appear somewhat paradoxical, we believe that this occurrence of polycythaemia, microcytosis, and a normal haemoglobin value, is the first sign of an iron deficiency anaemia. Such a view receives confirmation from the fact that sometimes in the course of the cure of nutritional anaemia of infancy by the exhibition of iron, what is known as Hagen's phenomenon occurs, i.e., before the haemoglobin reaches a normal figure the red cell count may exceed 6 million per c.cm. but when the haemoglobin does become normal the red cells become reduced to 5 million. The defects of this special diet are, however, even more strikingly shown by the animals in the succeeding generation because the pregnant rat on this diet is unable to transfer sufficient iron to the foetus, with the result that the progeny, during their lactation period, develop a severe degree of microcytic anaemia, a state of affairs which clearly shows that the diet of the mother during pregnancy and lactation has a direct bearing on the blood picture of her young. In previous papers (Parsons[11]. Parsons and Hickmans[12], Parsons and Hawksley[13]) the occurrence of congenital nutritional anaemia both in the rat and the human infant has been described, and the existence of such a condition has thus been confirmed by the present series of experiments. One important point of difference between the human mother and the rat has, however, been observed. The human mother can sacrifice her own haemoglobin for the sake of the child, and although becoming profoundly anaemic herself, more often than not gives birth to a child whose blood is normal, whereas in none of the rat experiments has any pronounced diminution in haemoglobin in the mother rat occurred. This congenital nutritional anaemia of the rat is microcytic in type and becomes progressively worse if milk feeding is continued beyond the lactation period. If, on the other hand, these anaemic rats are fed on the special diet herein described from the end of the lactation

period, the haemoglobin rises and polycythaemia develops but microcytosis remains—a blood picture identical with that of their parents.

Effect of administration of copper and iron on congenital nutritional anaemia

The anaemia and microcytosis in these rats of the second generation can be rapidly cured by the addition to the daily diet of ferrous sulphate (0·5 mgm. Fe) and a trace of copper sulphate (0·025 mgm. Cu); typical Price Jones' curves before and after such treatment are given in fig. 4 and show that the mean diameter increases from 5·73μ to 6.73μ.

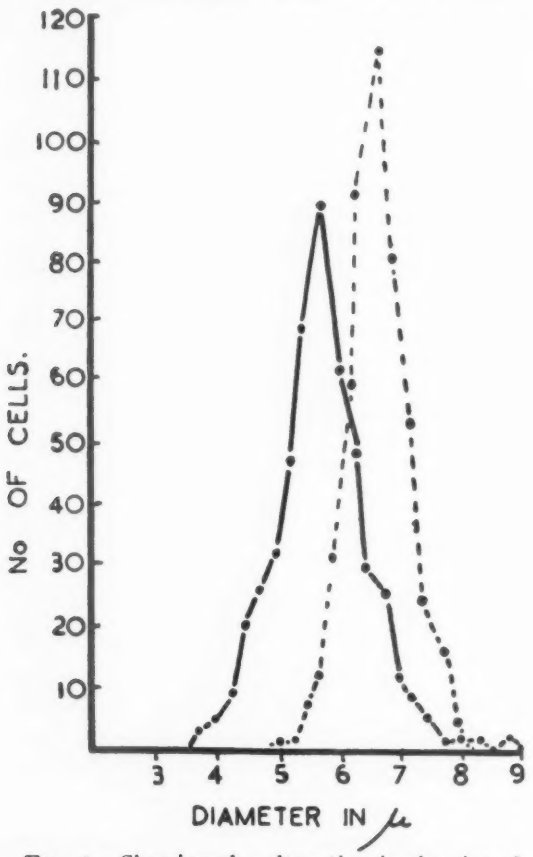

FIG. 4.—Showing the alteration in the size of the cells before and after treatment with $FeSO_4$ and $CuSO_4$.
Before, mean diameter = 5·73μ.
After, mean diameter = 6·73μ.

In some of their earlier papers Hart, Steenbock et al[7] stated that the administration of pure iron to rats suffering from nutritional anaemia did not produce a cure, but this invariably occurred if a small amount of copper was given in addition to the iron. In their opinion this was due to the exhaustion of both iron and copper stores in the bodies of the anaemic rats as the result of the deficient dietary. Later, Elvehjem and Sherman[3] showed that the administration of pure iron led to the accumulation of this element in the liver and that it was only mobilized for action by the subsequent administration of copper.

In the present experiments the rats were already anaemic during the lactation period and only a short time beyond the lactation period was

necessary to produce a severe anaemia. It was therefore thought that they might have retained sufficient copper stores to render the simultaneous administration of copper and iron unnecessary and attempts were made to cure the anaemia by the administration of ferrous sulphate only. Most of these were unsuccessful, but in three rats an erratic response with slow improvement occurred and the diameter of the cells eventually became normal. If, however, copper even in minute amounts (0·025 mgm.) was also given daily the return to normal was rapid and consistent. The differences between the response by these congenitally anaemic rats to pure iron and that to iron and copper in respect of haemoglobin, red cells and reticulocytes are shown by a series of graphs in fig. 5.

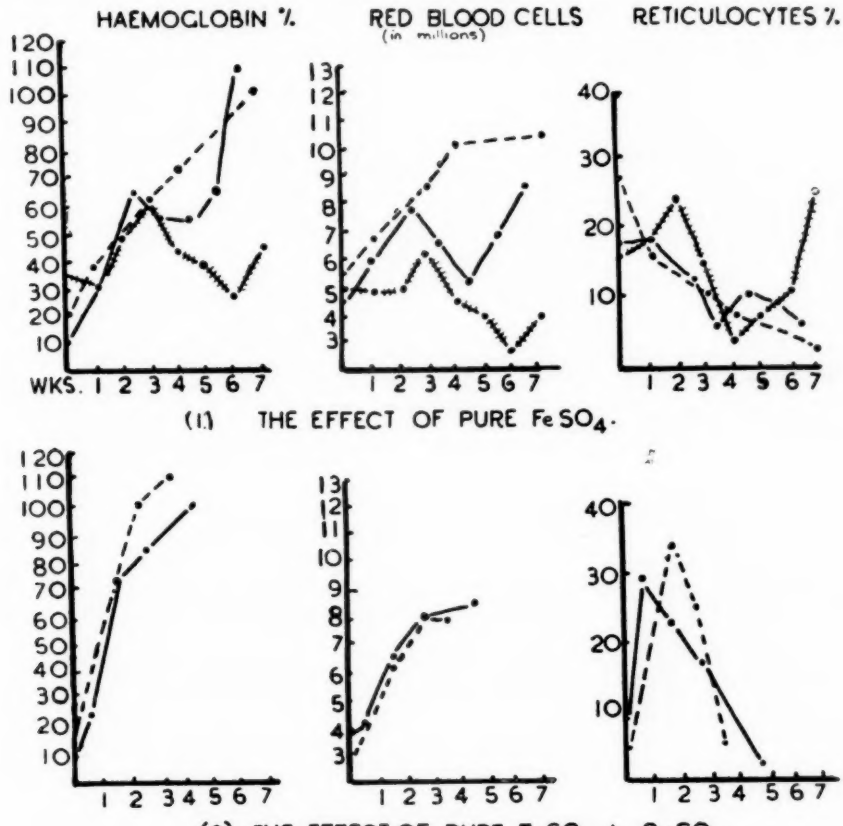
HAEMOGLOBIN %
RED BLOOD CELLS (in millions)
RETICULOCYTES %
WKS. 1 2 3 4 5 6 7
(1) THE EFFECT OF PURE $FeSO_4$.
(2) THE EFFECT OF PURE $FeSO_4$ + $CuSO_4$

FIG. 5.—Showing the effect on Hb., red blood cells and reticulocytes of anaemic rats of:
(1) Pure $FeSO_4$.
(2) ,, ,, and $CuSO_4$.

Effect of special low-iron diet on the breeding and growth of second generation rats

The first generation of rats fed on the special diet breeds fairly freely and may have three or four litters in the first eighteen months of life. (Some of the stock rats in the same colony may have eight or nine litters in the same time.) Most of these litters survive and grow up on this deficient diet to produce adult rats apparently identical with their parents. These, the second generation, however, breed with difficulty, their litters are few and

during the period covered by these experiments (two to three years) few have survived the lactation period; at about the eighteenth day of age they suddenly assumed the appearance of having had a bath or of having been immersed in their food and often were killed off by the doe. A few have, however, survived and the weights and haemoglobin values of some of the third generation rats are shown in the following table:—

Age of rats of third generation on iron-low diet.	Haemoglobin.	Average weight of one.	Average weight of one from stock litter.
Birth	45		
2 days		5 gm.	5 gm.
11 days	35	10 gm.	
16 days		12 gm.	19 gm. (14 days)
18 days	10	22–35 gm.	30–35 gm. (21 days)
8 weeks		36 gm.	96 gm.

Discussion and summary

In a perusal of the literature on experimental nutritional anaemia of the rat it is found that the occurrence of polycythaemia on a iron-deficient diet has been previously described by Eveleth, Bing and Myers[4].

These writers fed rats on a diet of raw cow's milk until they were anaemic; they were then given intraperitoneal injections containing sub-optimal amounts of pure iron, and as a result the rats not only developed a polycythaemia, but their haemoglobin remained subnormal throughout the experimental period. This would appear to be a stage nearer the typical nutritional anaemia than that shown by the animals in the present experiments, or in other words, the animals showed an earlier stage in the development of this iron deficiency anaemia. Eveleth et al. did not estimate the size of the red cells, and the only reference to microcytosis in milk anaemia in rats found is in the paper by Foster[5] already mentioned, who demonstrated a diminution in size of the red cells by the haematocrit method. Polycythaemia, marked microcytosis and a reduction of haemoglobin have, however, been demonstrated under apparently quite different conditions, namely as the result of an extreme restriction of all the inorganic constituents of the diet (Smith and Schultz[15], Swanson and Smith[18], Orten and Smith[9], Orten, Smith and Mendel[10]). The diet used in these experiments was extremely deficient in calcium and to a lesser degree in potassium, sodium, phosphorus, manganese, and chloride, and contained less iron than the albino rat is supposed to require. From a study of these contributions the cause of these blood changes was probably a deficiency in iron, and this view appeared to be borne out by the fact that when the Osborne and Mendel salt mixture, which contains adequate quantities of iron, was added to the diet the blood became normal. Orten, Smith and Mendel say that they also suspected that an iron deficiency was the explanation even though an ' iron deficiency usually produces a decrease in the erythrocyte content of the blood '—a statement shown in this paper to be incorrect provided that the iron deficiency is minimal—but that they were also struck by the deficiency of calcium in the diet and therefore planned a series of experiments to test the effect of administering iron and calcium to rats consuming such a mineral deficient ration. They found that the administration of adequate amounts of calcium (purified calcium carbonate in the amounts present in the Osborne and Mendel salt mixture) prevented the occurrence of these blood changes, or cured them if administered after the anaemia had been developed. Purified ferric chloride on the other hand, whilst preventing the development of the changes, showed variable results when used as a curative agent. These investigators also

found that sodium, potassium, manganese and chloride were not concerned in the production of the blood changes and came to the conclusion that the ' haematological abnormalities which occur in rats as a result of the feeding of the mineral deficient ration are due chiefly, if not entirely, to a lack of calcium and/or iron.'

Nevertheless, in spite of these findings, we are still of the opinion that these blood changes are essentially due to a deficient supply of iron to the bone marrow which, as stated at the commencement of this paper, is believed to be the essential cause of a microcytosis, and that the cause of this deficiency must be looked for in the inter-dependence of calcium and iron metabolism; and that the results obtained by these workers can be adequately explained on this ground. Both calcium and iron are absorbed from the same portion of the alimentary canal; both require an acid medium for adequate absorption and are therefore less readily absorbed if achlorhydria is present. Further, Brock and Diamond[1] showed that the administration of large amounts of iron will produce rickets in rats who are on a non-rachitogenic diet. It is therefore clear that the calcium-iron-phosphorus ratio in the bowel is an important factor in both calcium and iron absorption. In the ' poor salt diet ' the extreme deficiency is in calcium, whereas that of phosphorus and iron is relatively much less. In other words, there is a relative excess of phosphorus available to combine with the iron to form insoluble ferrous phosphate and thus to restrict a large portion of already somewhat deficient iron and phosphorus to the intestine and produce a real iron deficiency. Those who have worked with this dietary have themselves produced definite evidence in favour of this explanation in the observations made by Swanson, Timson and Frazier[19] that the blood changes are not so marked if edestin, a protein which contains little, if any phosphorus, is substituted for the phospho-protein casein in the ' poor salt diet.' It would have been interesting to see what would have been the result on the blood if the diet had been modified so as to be extremely deficient in phosphorus and less so in calcium.

An attempt has been made to apply these findings to clinical medicine. In coeliac disease, the absorption of calcium is greatly diminished. We therefore administered to children suffering from the hypochromic microcytic anaemia of that disease large doses of calcium chloride for a period of three to four weeks, and then for a further period calcium chloride and a minimal dose of iron—one-tenth of the usual dose—but without any significant effect on the anaemia.

Summary

The results of the investigations contained in this paper may therefore be summarized as follows:—

(1) A special iron-deficient solid diet has been devised which when fed to rats results in the development of polycythaemia and microcytosis although the haemoglobin remains normal—findings which it is suggested are the first step in the production of an iron-deficiency anaemia.

(2) The offspring of such rats develop in the lactation period an anaemia greater than the physiological anaemia of infancy and one which is microcytic in type.

(3) If these young rats, after weaning, are fed on the special diet, microcytosis persists, but polycythaemia develops and the haemoglobin becomes normal.

(4) If the diet of these young rats after weaning is restricted to milk the anaemia becomes progressively worse and the cells smaller and less numerous than those in the group receiving the special diet.

(5) The cells can be restored to normal size by the administration of adequate amounts of iron and a trace of copper.

(6) Rats fed on the diet for one generation can produce and rear their litters fairly well, but the reproductive powers of the succeeding generation fed on the same diet are greatly diminished, the young are reared with difficulty, are subnormal in weight and size and show an even more pronounced anaemia than the preceding generation.

(7) The analogies between these findings and certain clinical conditions in the human mother and infant are pointed out.

(8) The findings support the suggestion that the infants of women whose diets during pregnancy are low in iron or who suffer from an iron deficiency anaemia may show a congenital nutritional anaemia.

Acknowledgements

We wish to express our indebtedness to the Medical Research Council for a grant covering the expenses of the work and for a personal grant to one of us (E. M. H.).

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CONTINUOUS INTRAVENOUS DRIP IN INFANTS AND CHILDREN

BY

WILLIAM C. BLACK, M.D.

(From the Department of Pediatrics, Stanford University School of Medicine, San Francisco, California.)

Indications for continuous intravenous administration of fluids are perhaps more common in infants and children than in adults. The principal conditions in which the procedure is useful in paediatric practice are diarrhoea, persistent vomiting, severe burns, and states of severe dehydration and 'acidosis' associated with acute infections. The continuous intravenous drip used when the indications are definite is an invaluable therapeutic aid. It is the purpose of this paper to describe in detail the equipment and technique which give the most consistently good results. They vary only in a few details from the method described by Brush[1].

Description of equipment and technique

Materials and assembly :

1 250 c.c. graduated cylinder.
6 ft. black gum rubber transfusion tubing.
1 Murphy drip bulb.
1 connection tip to adapt the needle to tubing.
1 small calibre needle.
1 small, not graduated, plain ureteral catheter (No. 4 for babies, No. 5 or 6 for older children).
1 screw clamp.

A short piece (6–8 in.) of the tubing is connected to the bottom of the graduated cylinder and the screw clamp slipped over the free end. Then the Murphy drip bulb and the rest of the tubing are attached. The needle connection tip is inserted into the lower end of the tubing and all the connections are tied with linen thread. New tubing requires special preparation before use to prevent reactions. This consists of two-hour boiling in 1 per cent. sodium citrate solution, rinsing in 1 per cent. ammonia and finally thorough washing with tap water. This apparatus is sterilized, except the catheter, by autoclaving or boiling. A needle should be chosen which fits snugly into the catheter. The needle should be cut off square about one-half inch or a little less from the hub, and sterilized with heat. The catheter consists of a woven silk tube impregnated with a gummy distillate of linseed oil. It will not stand sterilization by boiling. Prolonged soaking is also deleterious. It is best sterilized by soaking it for fifteen minutes in a 1:1,000 solution of mercury oxycyanide. Following this it should with sterile precautions be flushed and washed with sterile water. This is most easily accomplished by means of a sterile Luer syringe and the cut needle

described above. The catheter can be slipped over the needle by means of sterile forceps and flushed. Then it is placed in a dry, sterile, covered dish until dry. One catheter so prepared is sufficient for eight or more pieces of suitable length. Each piece as it is cut should be about two and a half inches long. If it is cut with sterile scissors the remainder of the catheter need not be sterilized again (fig. 1).

Technique :

A sterile tray containing the following should be prepared:—

1 scalpel.
2 mosquito clamps.
3 towel clips.
1 scissors.
1 1½ c.c. Luer syringe.
1 hypodermic needle.
1 probe such as is used in dissection (for dilating the vein).
Yucca board, cotton, bandages, adhesive tape and novocaine should be available.

Success in the use of the continuous intravenous drip results from careful attention to certain details which in themselves are simple. In the following description an attempt has been made to include these details and to emphasize them properly. The rationale of their importance should be obvious if it is recognized at the onset that the aim of the procedure is to place the catheter in the vein with a minimum of trauma to the vein, a minimum of distortion to the natural course of the vein and to fasten the catheter in place in such a way that the child may move about and be moved without causing any change in the relation of the catheter to the vein—without rotation, pulling, pushing, or side traction.

Because of its constant position in practically all individuals, and its situation on the lower extremity where the attachment of this apparatus causes a minimum of inconvenience both to the patient and to those attending him the great saphenous vein where it runs across the ankle just anterior to the medial malleous is the vein of choice.

Cut a piece of yucca board to conform roughly with the size of the foot and pad it well on one side with cotton held in place with roller bandage. Fasten this in turn to the outer side of the foot (the padding next to the skin) with adhesive tape and bandage which is carried up nearly to the medial malleolus. The purpose of this is two-fold; to limit the motion of the ankle and to afford a means of restraining the foot during the procedure. By means of adhesive tape, or preferably safety pins, fix the foot to the table or bed in a position of external rotation. Now fill the cylinder and tubing with warm solution for injection being careful to have the fluid in the Murphy drip bulb at the correct height.

Scrub the hands and put on sterile gloves. Prepare the skin with iodine and alcohol and drape with three sterile towels held in place with the towel clips. Anaesthetize the skin with novocaine. Make an incision ½ inch long directly over and parallel with the course of the vein. The site of the incision may be previously marked by a pin scratch. The field should be brightly illuminated. Spread the tissue and strip the vein with the mosquito clamp. Then pass black silk ligatures under the upper and lower ends of the exposed vein but do not tie them. Lift the vein by means of the lower ligature and cut the vein about half in two with the scissors. If the vein is found to be quite small, dilation with the probe will facilitate entrance of the catheter. Further, if the end of the catheter itself is cut obliquely it will enter the vein more easily. In small subjects passage of the catheter

occasionally requires a little patience but the vein is quite distensible and will accept a catheter which at first may appear to be much too large. The catheter should be wet before it is inserted and should be pushed into the vein about one inch. Now tie the proximal ligature firmly around the vein and catheter. It is well to anchor the ligature by bringing it back and tying it around the needle hub. The latter should be so placed in the

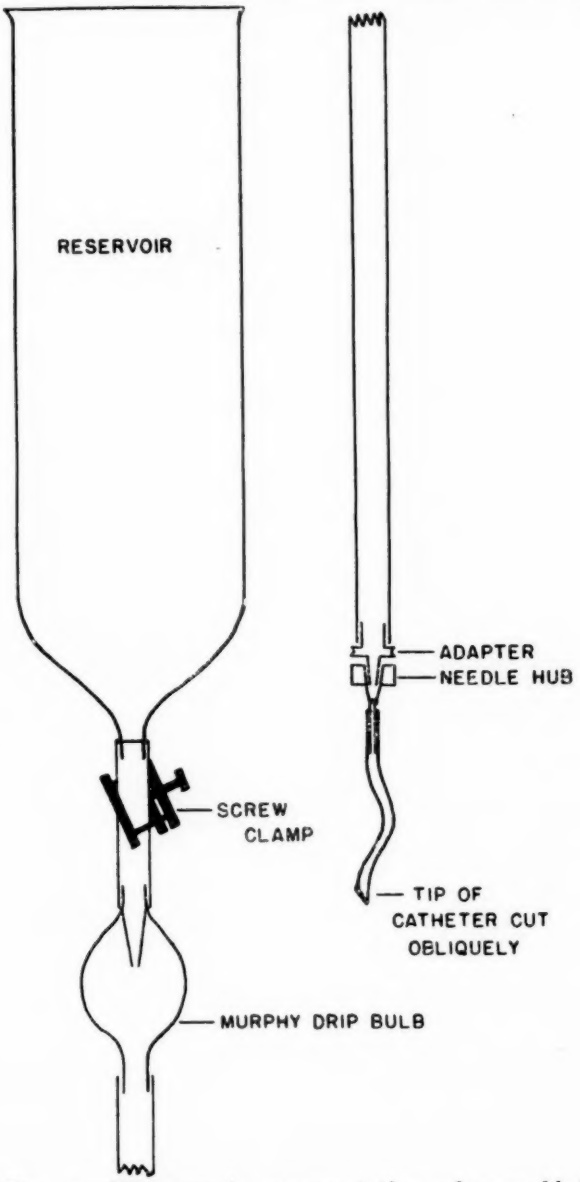

FIG. 1.—Diagramatic representation of assembled continuous intravenous drip apparatus.

catheter that the flat side of the hub lies flat against the skin without any torsion of the catheter. Twisting the catheter twists the vein and will cause stoppage of flow. With a Luer syringe run in five or ten c.c. of sterile saline to prove the patency of the system. Then tie the lower ligature around the vein and cut one end short and one end long so that at the termination of the drip this ligature may be removed easily without opening the wound.

Connect the previously filled tube with the needle and permit the fluid to drip in fairly rapidly. Fasten the needle hub firmly against the skin with adhesive tape. Leave the wound open but cover it with a sterile dressing. Free the foot and yucca board and wrap foot, yucca board, tubing and all with cotton batting and bandage liberally but not too tightly, being especially careful not to have any bandage pressure above the point of entrance of the catheter into the vein as this will obstruct the flow. Of equal importance is to prevent any traction or torsion of the tube which would be transmitted to the catheter. By fastening the tube firmly with adhesive tape where it emerges from the bandage any unexpected traction on the tube will be transmitted not to the catheter but to the bandages.

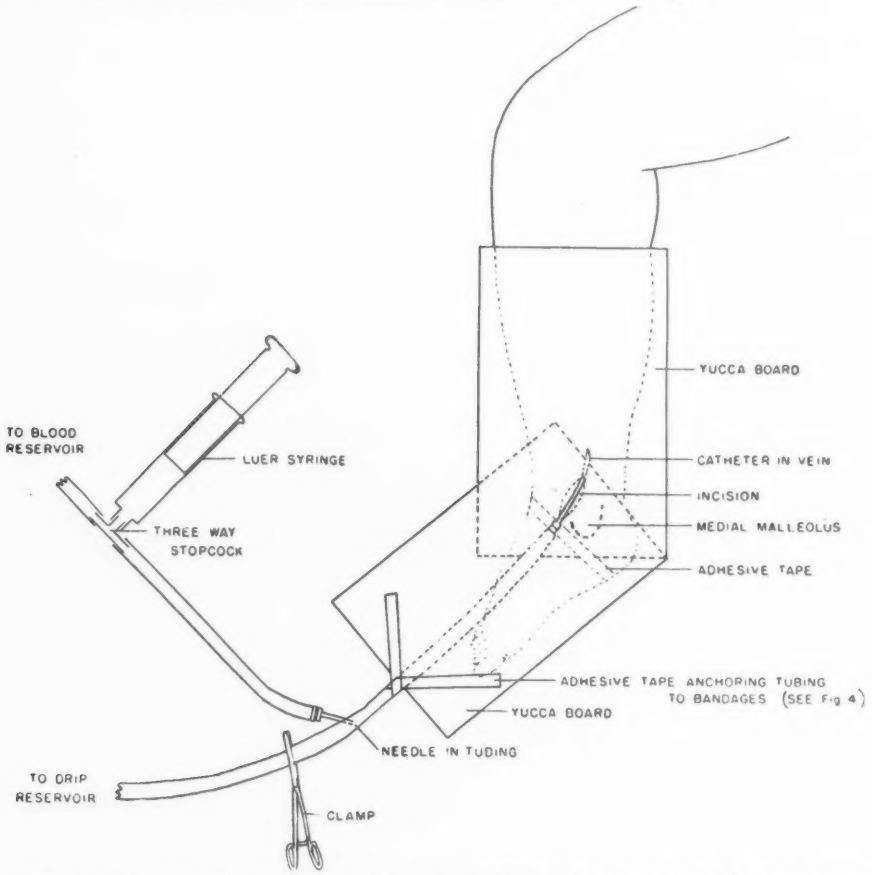

FIG. 2.—Diagramatic representation of continuous intravenous drip apparatus in use and the means by which a citrated blood transfusion may be given.

Adjustment of the rate of flow is accomplished by means of the screw clamp on the tubing above the Murphy drip bulb. When children or infants cry the venous pressure is temporarily raised. If the Murphy drip bulb is not kept three or four feet above the level of the ankle, during these rises of venous pressure a little blood may regurgitate into the catheter, coagulate and obstruct the system. If the drip bulb fills and the drops cannot be counted cleanse the tubing just below the drip bulb with iodine, and with a smaller needle and Luer syringe pierce the tube and slowly inject air into the bulb to displace the fluid. It should be injected just fast enough to stop the drops. It is well to keep the solution warm by means of an electric pad or hot water bottles. At low rates of flow this is of minor importance.

Hypertonic solutions* are irritating to the wall of the vein and are prone to cause thrombosis. If they are used they should be alternated with isotonic solutions. If the drip slows down unexpectedly disconnect the tube and aspirate the catheter with a Luer syringe. This will often re-establish a free flow, apparently by dislodging a tiny flake of fibrin. If transfusions are to be given while the drip is in use the blood may be injected through the catheter. This is most conveniently accomplished by clamping the tubing an inch or two distal to the point where it emerges from the bandages. Sterilize the rubber tubing between the clamp and the

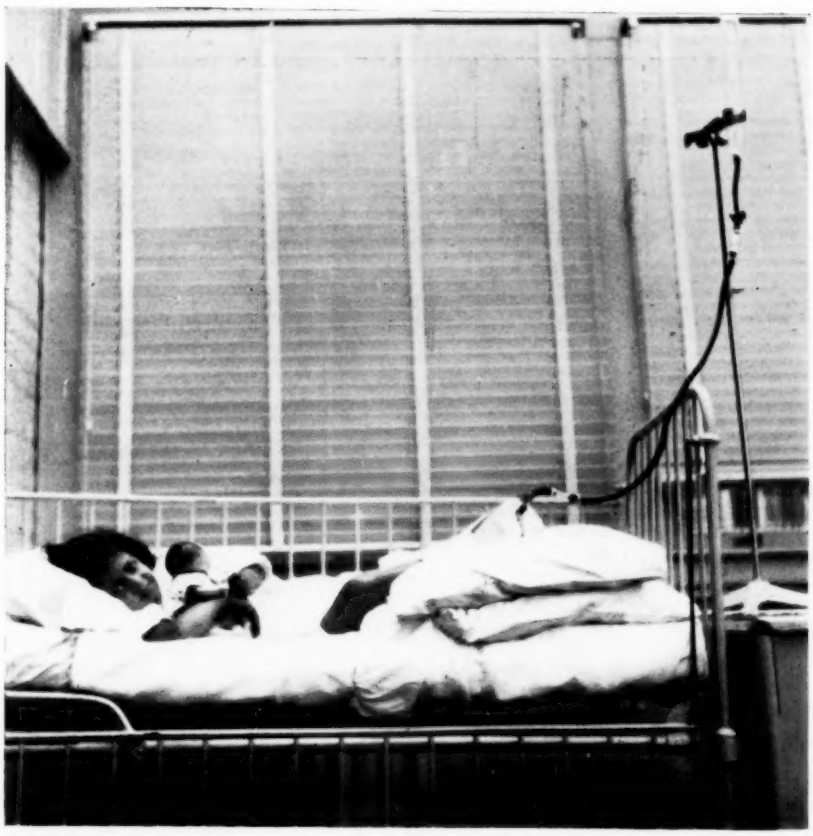

FIG. 3.—Continuous intravenous drip apparatus in operation. Note elevation of foot above level of base of heart.

bandages with tincture of iodine, puncture the sterilized tubing with the needle from the reservoir of citrated blood and permit the blood to run in either by gravity or by positive pressure with a Luer syringe connected with a three-way stopcock inserted between the needle and the tubing containing blood. The hole in the tubing will seal itself when the needle is removed. When the clamp is removed the drip will resume function (fig. 2).

* Five per cent. glucose, 0·9 per cent. sodium chloride, and 1/6 molar sodium lactate are all isotonic. When a combination of these is to be used only isotonic solutions should be mixed if the resultant solution is to remain isotonic.

Discussion

Results with the continuous intravenous drip have been improved in recent months by the adoption of two simple points which diminish the tendency for blood to regurgitate into the catheter and coagulate. First the patient's foot is kept elevated by means of pillows several inches above the level of the base of the heart as much of the time as possible. Second, the nurse is instructed to open the stopcock to permit a maximum rate of flow for a few seconds every hour (fig. 3 and 4). When the drip is dis-

FIG. 4.—Continuous intravenous drip apparatus in operation. Note anchoring adhesive tape (stained darkly), liberal bandaging of foot and leg and absence of tight bandaging above the incision.

continued (and it can run for three days or longer if desired), the two ligatures are gently cut away from the vein and a fairly firm moist dressing applied in such a way that the edges of the wound are approximated. The vein probably becomes patent again eventually.

That the continuous intravenous drip has inherent dangers cannot be denied. They are: (1) sudden flooding of the circulation; (2) air embolism; (3) wound infection; (4) thrombosis and embolism. The first two are

entirely preventable. The third, wound infection, may occur occasionally even when proper antiseptic precautions are taken. That infection is of infrequent occurrence is attested by the fact that we have not seen a single instance of it. Thrombosis and embolism probably occur more frequently than they are recognized. Rumold[2] offers experimental evidence to support this view. Induration and tenderness over the vein have occasionally been noted proximal to the site of attachment of the apparatus which persists for several days after discontinuing the drip. This is more likely to occur if hyper- or hypotonic solutions are employed. Orr[3] reported a case of pulmonary embolism following the use of an intravenous drip and gleaned several other instances from the literature. Hence a word of caution must be offered: if the flow should stop do not attempt to clear the obstruction by applying positive pressure. It is only permissible to aspirate gently and if this is unsuccessful either to remove the catheter and replace it with a new one or to choose another vein and make a fresh start.

After functioning well for several days the flow occasionally may gradually become less free and eventually stop. This is often caused by gradual swelling of the catheter, probably from absorption of water, as also occurs when the same type of catheter is left for several days in the pelvis of the kidney for continuous drainage and irrigations. Despite this disadvantage we prefer the catheter to a metal cannula because the former is much less apt to irritate the wall of the vein and lead to occlusion. Furthermore a considerable degree of freedom of motion of the leg and foot is permitted. This latter feature is of great importance from the standpoint of the comfort of the patient, in facilitating turning of the patient and other features of nursing care.

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NOTICE

In 1938 the ARCHIVES OF DISEASE IN CHILDHOOD will be issued quarterly, instead of bi-monthly, in March, June, September and December. The number of pages in each number will be increased so that the complete volume will be of the same length as heretofore.

Beginning with the issue in March, 1938, references will be arranged on the Harvard system and the attention of contributors is called to the details of the revised system set out on the inside page of the front cover of this number.

CASE REPORTS

ATROPHIC CIRRHOSIS OF THE LIVER
following
ICTERUS GRAVIS NEONATORUM

BY

FRANCES BRAID, M.D., M.R.C.P.

WITH PATHOLOGICAL REPORT

BY

J. H. EBBS, M.D., D.C.H.
(From the Children's Hospital, Birmingham.)

Cirrhosis of the liver is a comparatively rare disease in childhood. Poynton and Wyllie[1] describe seven 'types,' one of these being a type associated with icterus gravis neonatorum. They say:—

Pathologically, there may seem to be very little evidence in favour of grouping such cases among cirrhoses of the liver. In affected infants dying in the first few days after birth . . . (there was) found no indication of increased connective tissue. . . . In the more chronic cases, however, as in the fourth child in Pfannenstiel's family which died on the 21st day, the liver was enlarged, coarse and dark green . . . Microscopically, the interstitial tissue of the liver was irregularly broadened and had an oedematous appearance, with here and there small collections of cells. The liver cells contained bile and the cell columns were very narrow; the bile ducts were widened at several points. These details are strongly suggestive of an early biliary cirrhosis, the fibrosis not commencing till after birth.

This thesis is supported by Hawkesley and Lightwood[2] in their clinical and pathological study of icterus gravis neonatorum. They found, in seven cases out of nine of more than five weeks of age, signs of hepatic fibrosis. The fibrosis was most conspicuous in relation to the portal tracts but an intercellular fibrosis was also observed. They suggest that survival from icterus gravis may be accompanied by cirrhotic changes in the liver and that infants so surviving may become the subjects of multilobular cirrhosis of the liver in early childhood.

Several cases of liver cirrhosis with a history of jaundice in the neo-natal period have been reported. The patient reported by Smith[3] at the age of

four-and-a-half years was jaundiced in the first six weeks, Bossert's[4] patient for seven weeks and Curtis'[5] patient, age fourteen years, had a 'rather severe type of jaundice neonatorum but it cleared perfectly.' In de Lange's[6] case which died at the age of seven months jaundice had been present from the third day of life. These authors either do not discuss the possible relation between the two conditions or suggest that some congenital defect of the liver may have been present. Bossert, for instance, thinks that the early icterus lends some support to this theory but feels that its disappearance makes acceptance improbable. But Hanau[7], who gives the most detailed description of his case, discusses fully the type of the neonatal jaundice and its possible relation to the cirrhosis which developed. The main points in his case are these:—

The child was the eighth in a family of eight of whom only two survived. Of the others, two were stillborn, one died at seven weeks of convulsions, one died during the first year of some unknown cause and one was a premature still-birth. The maternal Wassermann reaction was negative. This child was jaundiced during the first three months of life and enlargement of the liver and spleen was noted during the first month. At one year and nine months, the liver and spleen were large, the abdominal veins distended and ascites was present. The course of the illness was then rapidly fatal. At autopsy, the liver was found to be nodular and the entire surface granular. The large bile-ducts were patent. Microscopically, the lobules were bordered by thick connective tissue in which were clumps of lymphocytes. There was fatty infiltration and degeneration of the liver cells. Hanau discusses fully the differential diagnosis of the neonatal jaundice and concludes that it belonged to the familial icterus gravis group. Although he could find no account of the fate of recovered cases of icterus gravis he considers it to be a possibility that the cirrhosis was a direct sequel to the icterus in his case.

The patient who is the subject of the present report is of interest because she first came under observation in the neonatal period suffering from icterus gravis and died at the age of three-and-a-half years from haematemesis due to multilobular cirrhosis of the liver.

Case Report

First admission. The patient, a female born on March 4, 1933, was admitted to the Children's Hospital at the age of four weeks with the history that since the age of three days she had been jaundiced and had passed colourless stools. She was the second child of healthy parents and the first child was healthy. On admission, her general condition was good and her weight was 8 lb. 11 oz. She was deeply jaundiced. The liver was enlarged and at this time the spleen was not felt. The stools were colourless. No umbilical sepsis or other abnormality was noted.

Laboratory Investigations

Blood. The van den Bergh test gave an immediate direct positive reaction, the indirect reaction showed 2·0 units of bilirubin. The fragility of the red cells was normal. The total red cells were 3·9 million, Hb. 74 per cent., C.I. 95, reticulocytes 5·8 per cent. (age 9 weeks), total white cells 11,500; polymorphs neutrophil, segmented, 16·5 per cent., non-segmented,

8 per cent.; eosinophil, segmented, 0·5 per cent., non-segmented, 1·5 per cent.; myelocytes 1 per cent.; metamyelocytes 0·5 per cent.; lymphocytes 70·5 per cent.; plasma lymphoblasts 0·5 per cent.; monocytes 1 per cent. The red cells stained well and were uniform in size; halometer reading 4·5=7·64μ (at age 4 weeks).

Stools. Bile pigments were absent, bile salts present.

X-ray examination of the long bones showed no evidence of congenital syphilis. The maternal Wassermann reaction was negative.

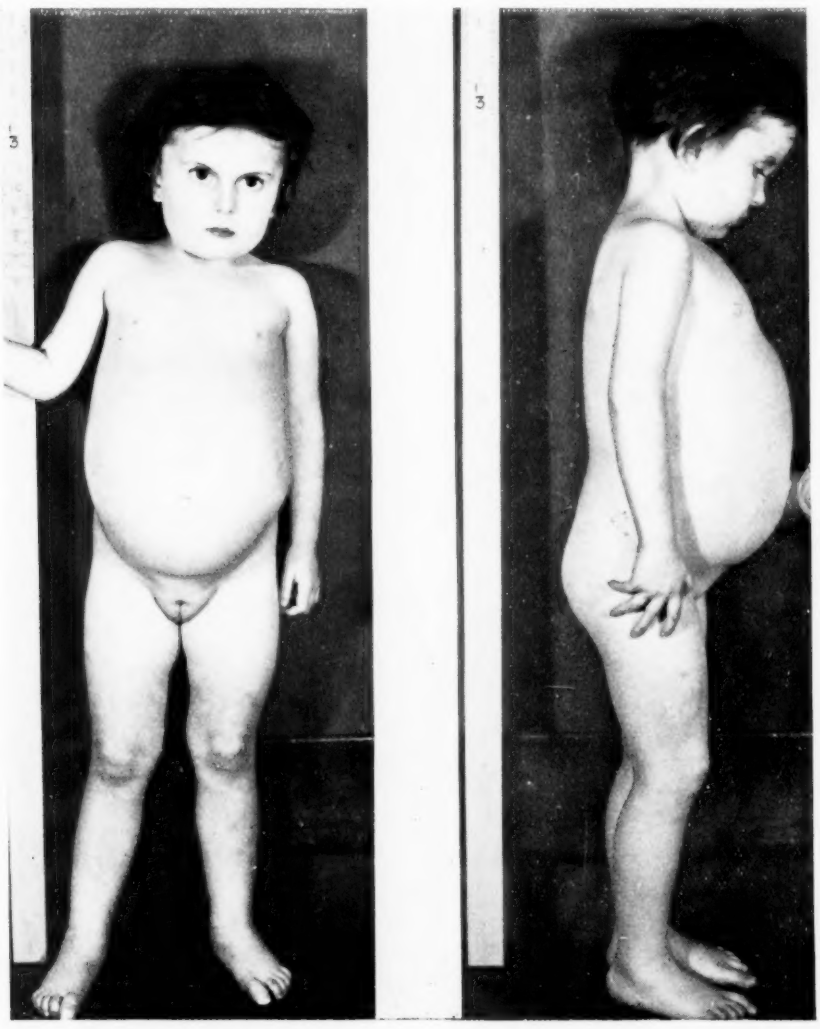

Fig. 1.

Progress. On 18.4.33, the stools contained some bile pigment and from 25.4.33, when aged seven weeks, normally coloured stools were passed. The jaundice then gradually lessened. The baby maintained her good general condition and lost only 8 ounces during the first three weeks in hospital and then gained weight slowly. She was breast fed. On 4.5.33 she was discharged, still jaundiced and with the liver enlarged to the level of the umbilicus. Observed in the out-patient

department, the jaundice cleared steadily and completely, the liver remained large and the spleen became palpable at the age of five months. At eight months blood examination showed total red cells 4·3 million, Hb. 90 per cent., C.I. 1·04; total white cells 6,050 with a normal differential count. The general health and progress of the baby were good. In July, 1934, she had a severe attack of whooping-cough, complicated by pneumonia from which she made an apparently good recovery. At this time the liver was still enlarged and the spleen palpable.

Second admission. On 17.11.36 (aged $3\frac{1}{2}$ years) she was again brought to the hospital because of enlargement of the abdomen which had become apparent in the previous fortnight. Until then her general health had been good and her physical and mental development normal. Examination revealed a marked enlargement of the abdomen with distended superficial veins (fig. 1). Much free fluid was present. The liver was now small, hard and nodular, felt in the intercostal angle below the xiphisternum but not felt under the costal margin in the mid-clavicular line. The spleen was palpable and the area of splenic dullness was increased. There was no jaundice at this time. There was no evidence of any lesion of the central nervous system. X-ray examination showed no abnormality of the bones.

Laboratory investigations

BLOOD. (23.11.36.) The van den Bergh test showed a direct negative reaction, indirect reaction 0·4 units of bilirubin; takata-ara reaction positive; albumin 2·94 per cent., globulin 1·65 per cent., calcium 8·9 per cent., phosphorous 4·2 per cent; phosphatase 18·0 mgm. P. liberated by 100 c.c. serum during three hours' incubation at 37° C. Intravenous glucose test (25.11.36) showed impaired tolerance.

URINE. (26.11.36.) Urobilin and urobilinogen in excess, bile pigments and bile salts absent.

STOOLS, average of three days. Dried faeces 66 gm.; total fat 32·1 per cent., unsap. fat 19·1 per cent., sapon. fat 13·1 per cent., free fatty acid 13·1 per cent., neutral fat 5·9 per cent., daily output 4·2 gm.

Progress. A suspicion of jaundice appeared on 27.11.36; on the two following days there was a sudden unexplained rise in temperature associated with diarrhoea. On 30.11.36, she had a severe haematemesis and died within twelve hours of its onset and within four weeks of the appearance of gross signs of liver failure

Pathological examination

The body was that of a three-and-a-half year old female child, well nourished with a slight excess of superficial fat. The skin and mucous membranes were extremely pale and slightly jaundiced. Prominent, tortuous veins were visible beneath the skin of the abdominal wall.

Both pleural cavities contained a small quantity of slightly bile-stained fluid. The lungs showed evidence of terminal congestion but no other disease. The remainder of the thoracic contents, including the heart, presented no abnormalities.

The peritoneum appeared healthy and contained a small quantity of bile-stained ascitic fluid. The liver was slightly enlarged, measuring 16·2 cm. by 10 cm. and 7·5 cm. in thickness. The whole organ was grossly nodular (' hobnail '), firm, and presented small granular nodules superimposed on the surface of the large knobs. The external surface was pale, with large gray streaks in an otherwise mottled surface, punctuated by scattered dark haemorrhagic areas (fig. 2 and 3). The gall bladder appeared

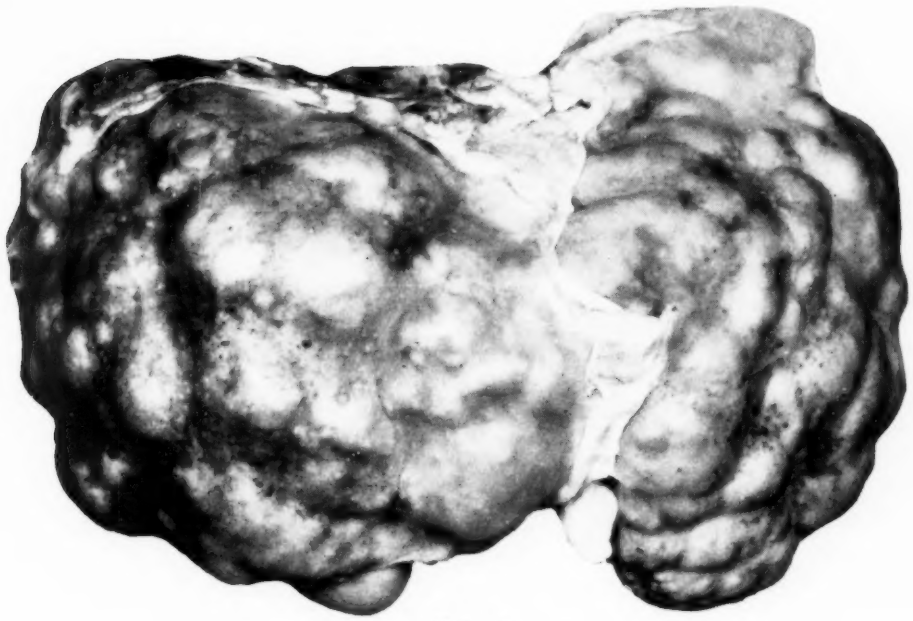

FIG. 2.

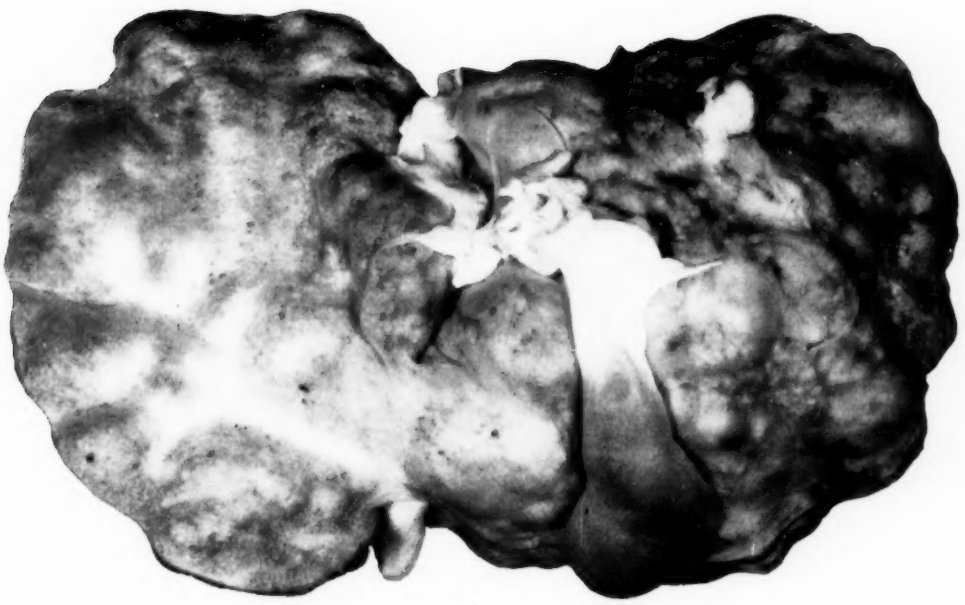

FIG. 3.

normal in size and contained normal bile. The cystic duct was patent and surrounded by an abnormal amount of fibrous tissue. All ducts were patent. The cut surface of the liver showed marked fibrosis with a multilobular distribution (fig. 4).

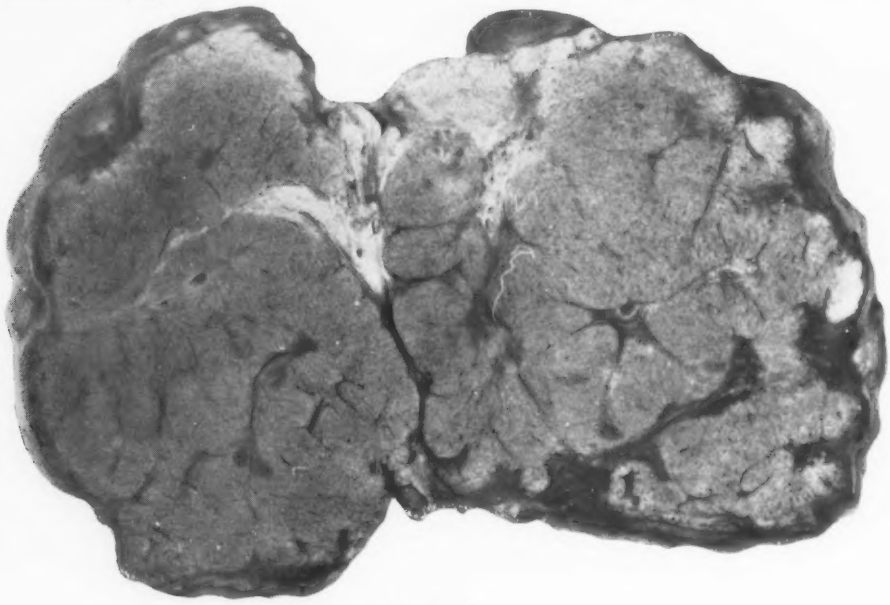

FIG. 4.

The spleen was slightly enlarged, measuring 10·5 cm. by 7·5 cm. and it was firm and moderately fibrotic (fig. 5).

The lower end of the oesophagus contained several dilated, tortuous vessels. The site of rupture of the varices which resulted in fatal haemorrhage could not be found (fig. 6).

FIG. 5.

FIG. 6.

The brain showed no evidence of bile staining. The bone-marrow of the femur was red, and appeared normal. Smears and sections of this showed no abnormality.

Microscopical examination of the liver revealed a coarse multilobular cirrhosis, with very little damage to the liver cells (fig. 7 and 8).

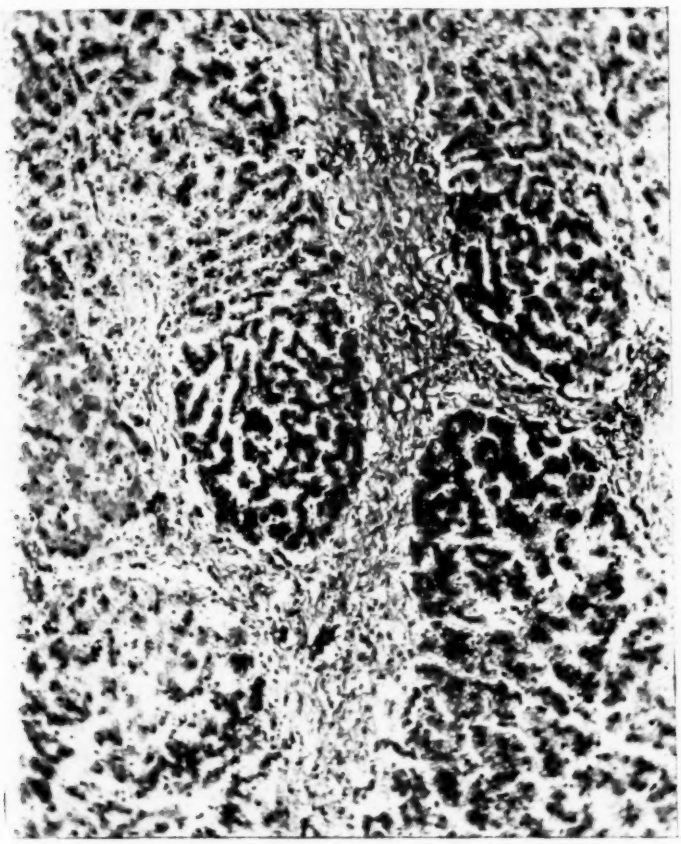

FIG. 7.

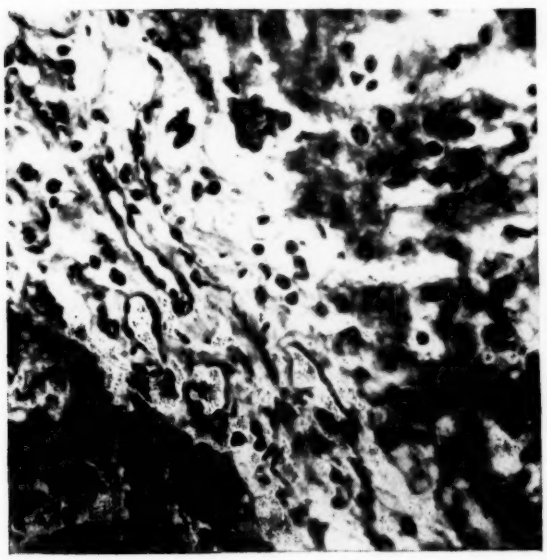

FIG. 8.

Discusssion

The jaundice in the neonatal period was not due to sepsis for there was no evidence of sepsis, no haemorrhage and no disturbance of temperature and it was not due to congenital syphilis for the maternal Wassermann reaction was negative and the infant's bones showed no evidence of syphilis on x-ray examination. Nor was the good general condition of the baby consistent with either of these diagnoses. Because of the absence of bile from the stools in the early weeks the possibility of congenital obliteration of the bile-ducts had to be considered. Blood examination did not support this diagnosis and the fact that bile entered the intestine after the age of seven weeks and the jaundice then disappeared, ruled it out entirely. Familial icterus gravis may appear in a form which is not acute and may be associated with a temporary acholia, and it is to this category that the jaundice of the case under review belongs. There is no family history of icterus gravis for she was only the second child and as is usually the case the first child was healthy. Blood examination supports the diagnosis of icterus gravis in the increased amount of circulating bilirubin and in the presence of reticulocytosis. The colour index was still above unity at the age of seven months. The diameter of the red cells, at age four weeks, was 7·6μ as compared with van Creveld's normal average of 8·266μ at that age. A fall, more rapid than normal, in the size of the red cells in icterus gravis neonatorum has been noted by van Creveld and by Hawkesley[2]. Subsidiary changes in the white cells were also present. The fragility of the red cells in icterus gravis is variable and in this case it was normal.

A temporary acholia in familial icterus gravis is an interesting fact. It was present in two of Hawkesley's cases in which early signs of liver cirrhosis were found and has been present in several cases under the care of one of us (F. B.). It was an outstanding feature in a patient who later developed generalized osseous dystrophy[8]. It was also present in another patient who has developed green teeth and in a baby now under under observation. The explanation of its occurrence is not clear. It may be a direct result of excessive haemolysis whereby the bile channels or the liver cells are overtaxed with excretory work or the bile pigments accumulate in the bile capillaries. If that were so, one would expect to find a direct relationship between the extent of the haemolysis, as estimated by the degree of anaemia, and the absence of bile pigments from the stools. In our experience that is not so. In cases in which the red cells have fallen to one million or less acholia has not been observed and in those quoted above in which acholia has been a marked feature anaemia has not been severe. In the case under review the anaemia was slight and the fact that the spleen did not become palpable till the fifth month also suggests that haemolysis was not an urgent feature and not likely to be responsible for the acholia either by increasing the viscidity of the bile or by blocking the capillaries with pigment. Diamond, Blackfan and Baty[9] who regard icterus gravis and the conditions allied thereto as a result of a congenital metabolic defect of the haematopoietic system, believe that the acholia is due to over-

crowding of the liver with haematopoietic foci which cause pressure of the liver cells sufficient to cause an obstructive as well as a haemolytic form of jaundice. If that is so, and if the view is confirmed that these foci may be sufficient to cause obstructive jaundice in cases in which haemolytic anaemia is not severe, then it would give support to the idea that the excess erythroblastic tissue is a primary condition and not secondary to the haemolysis, as is more generally believed at the present time.

The cause of the cirrhosis of the liver in this case is not to be found among the recognized causes of cirrhosis of the liver in childhood —syphilis, alcohol, malformation of the bile-ducts—but in the icterus gravis or rather in the etiological factor upon which the occurrence of icterus gravis depends and that is still a matter for conjecture. It is familial and it may be a hereditary or a congenital defect or both. Hawkesley[2] mentions one case in which hereditary transmission is apparent and in some of the reported cases already quoted associated congenital defects are noted. In Bossert's case[4] bilateral congenital cataract was present, in the case reported by Curtis[5] there was congenital dislocation of the left hip-joint and in the case reported by de Lange[6] there was transposition of the viscera. It seems probable that there may be some link between liver cirrhosis following the familial condition of icterus gravis and juvenile familial cirrhosis, and the possible resemblance between ' kernicterus,' a complication of familial icterus gravis, and Kinnier-Wilson's familial disease, progressive lenticular degeneration[10] associated with atrophic liver cirrhosis, has often been suggested. The course of the illness is vairable in cases belonging to each of these groups but the type of the cirrhosis appears to be the same in all. In the case under review the liver was in the atrophic stage of multilobular cirrhosis, Bossert and de Lange considered their cases to be in the hypertrophic stage of atrophic cirrhosis, in the case reported by Curtis the liver was atrophic and in Smith's case the cirrhosis was interlobular in distribution. In Kinnier-Wilson's disease the cirrhosis is of this same type and this is true also of the cases of juvenile familial cirrhosis reported by Bramwell[11], and by Ruh and Albrecht[12] and Schuscik[13], and by others. Bramwell's cases are of especial interest. Although nervous signs were absent and although the clinical course was short compared with the chronic illness in the former group, he considers that his cases are similar to those described by Kinnier-Wilson. Barnes[14] supports this opinion in the group of cases which he reports. In two of his three cases belonging to one family haematemesis and gastro-intestinal disorders had actually occurred weeks or months before the nervous symptoms and, in the third case, gross signs of liver cirrhosis were present and at the time of the report evidence of a lesion of the central nervous system was absent. This makes the time factor in the appearance of the various signs in ' kernicterus ' of less importance in relating that condition to progressive lenticular degeneration.

Parkes Weber[15] places juvenile familial cirrhosis of the liver and progressive lenticular degeneration associated with cirrhosis of the liver among what he calls 'congenital-developmental disorders,' 'congenital' because the predisposition is in-born and 'developmental' because signs of the disorder appear at one or other stage of post-natal development. If further proof can be found to support the theory of Diamond and Blackfan that icterus gravis is due to some inborn metabolic defect of the haematopoietic system, then a relationship between icterus gravis with its sequels of 'kernicterus' and liver cirrhosis on the one hand and juvenile liver cirrhosis with or without progressive lenticular degeneration on the other hand might be established. They may be variations of a common 'congenital-developmental defect.'

Summary

(1) A case of cirrhosis of the liver following icterus gravis neonatorum is recorded.

(2) No lesion of the central nervous system or of the bones was present.

(3) The possible relation to juvenile liver cirrhosis and to progressive lenticular degeneration is discussed and it is suggested that familial icterus gravis may be classed with these as a congenital developmental defect.

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HYPERTROPHIC PYLORIC STENOSIS WITHOUT SYMPTOMS

BY

LEONARD FINDLAY, M.D., F.R.C.P.

B. D., a male aged four weeks, the second child of healthy parents, was admitted to the Princess Elizabeth of York Hospital for Children on May 8, 1937, because of ' peeling of the skin ' of two weeks' duration and vomiting after feeds for one week. The child was reported to have appeared healthy at birth and to have had a weight of 6 lb. 1 oz. He was breast-fed and seemed to make good progress until the age of twelve days, when the mother noticed ' peeling of the skin ' round the mouth, which thereafter gradually extended over the face and head and on to the trunk and limbs.

At the age of three weeks he ceased to put on weight and in consequence the question of insufficient breast milk was raised, but weighing before and after a feed showed an increase on the average of 3 oz. Nevertheless, extra-feeding was started in the form of a dried milk but this the child promptly and invariably vomited, not forcibly according to the mother's story but simply being ' brought up with wind.' The bowels continued to move regularly twice or thrice daily.

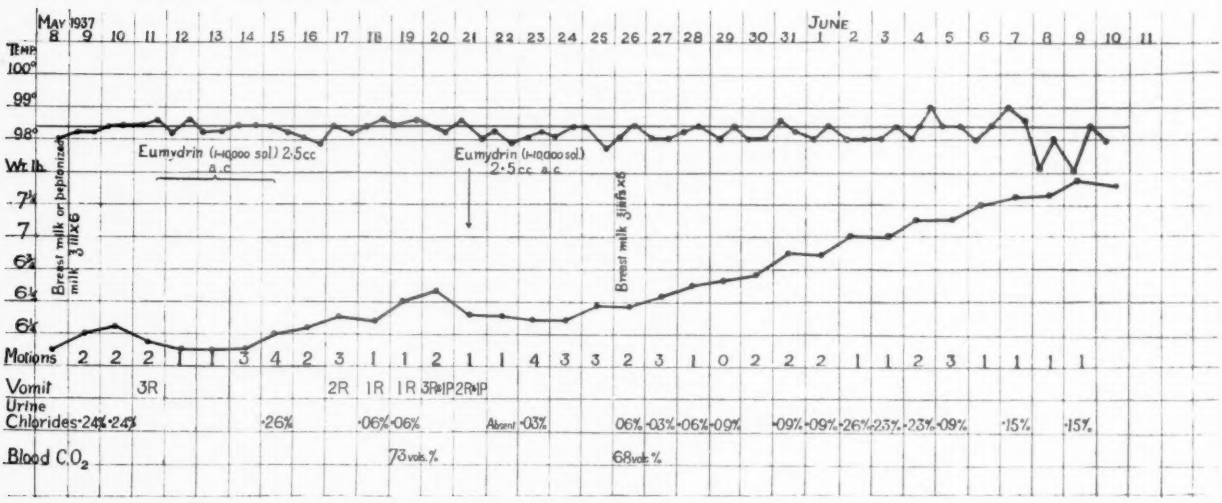
On admission to hospital the child had a weight of 6 lb. There was generalized desquamation of the skin except round the mouth, where it had started and where the skin had a pink colour, was quite smooth and delicate-looking as is seen in the floor of a recently ruptured blister. The skin of the face and body generally had a rather curious appearance. It was whitish and taut and drawn into wrinkles and suggested that the body had been covered with a thin layer of collodion. Wherever the skin had desquamated the exposed dermis was red and delicate-looking but it did not seem that any further peeling would take place, and this in fact was the course of events.

The mouth was normal except for slight enlargement of the tonsils and congestion of the pharynx. The chest was normal. On examination of the abdomen a pyloric tumour was easily palpable and gastric peristalis visible. A barium meal showed great interference with motility of the stomach; no passage of barium from the stomach was noted within three-quarters of an hour and complete emptying had not occurred by the end of seven hours. The urinary chlorides were 0·24 gm. per cent. Wassermann reaction in mother and child was negative.

In view of the physical signs a diagnosis of hypertrophic pyloric stenosis was made in an infant the subject of dermatitis exfoliativa. The question of ichthyosis vulgara was considered because the mother reported that in some of her relatives a dry scaly skin had been a marked feature. Two of her cousins, indeed, were said to suffer from the condition at present, although it was worse during their childhood and was responsible for their being sent home from school because of a ' dirty skin.'

For the first three days of residence in hospital the child was given breast-milk (3 oz. every four hours) when available, and if not the feed consisted of an equal quantity of peptonized milk. The skin was anointed with olive oil. During this time there had been no vomiting and the bowels had moved regularly. On the fourth day, however, but probably because

of a rather prolonged physical examination for the purpose of demonstrating the pyloric tumour and gastric peristalsis, vomiting did occur. This was more of the nature of regurgitation and was definitely not expulsive. Nevertheless, because of this development in the presence of a hypertrophied pylorus, eumydrin (1 in 10,000 solution, 2·5 c.c. half-an-hour before each feed) was instituted, but as there was no recurrence it was stopped after four days. However, within a further forty-eight hours the regurgitation of the feeds started again, taking place several times daily, but the bowels continued to move regularly and the weight steadily to rise. Within twenty-four hours of the onset of this latter spell of regurgitation the urinary chlorides, which had previously ranged between ·24 and ·26 gm. per cent., fell to ·06 per cent., the blood chlorides were reduced to ·404 gm. per cent. and the blood CO_2 registered 73 vol. per cent. The rejection of some of the feeds continued for five days; for the first three it was described by the nurse in charge as merely regurgitant in nature but on each of the fourth and fifth days the child had one expulsive vomit. At the end of this period chlorides were absent from the urine. The great bulk of the food, however, must have been retained as the motions, one or two daily, were of a normal character. Moreover, the child did not look ill and there was no evidence of depletion although he did lose weight slightly. In consequence of the return of the vomiting the eumydrin was again instituted (2·5 c.c. of a 1 in 10,000 solution before each feed), but from then until the child's dismissal from hospital, three weeks later, there was no recurrence of vomiting or regurgitation and he steadily increased in weight. During the residence the condition of the skin gradually became normal with no return of the desquamation. Details regarding the temperature, weight, feeding, medicinal treatment, vomiting, bowel action and urinary chlorides are shown in the accompanying chart (fig. 1).



R = Regurgitant. FIG. 1. P = Projectile.

Comment

It may be objected that the designation ' pyloric stenosis without symptoms ' given to the above case is unwarranted, but the symptoms were so slight (real expulsive vomiting only occurred on two occasions), the bowels moved daily, and the child never appeared ill, that the symptoms could hardly have been less prominent unless they had been absent

altogether. It is almost unknown for the vomiting in pyloric stenosis to intermit for more than twenty-four hours after it has once appeared, whereas in this patient this was the case for a period of more than seventy-two hours. Yet that hypertrophic pyloric stenosis was present there cannot be the slightest doubt. During the whole period (four weeks) that the child was under observation in hospital a pyloric tumour was palpable and peristaltic waves in an apparently dilated stomach were invariably observed after a feed. Furthermore, the result of the barium meal presented the characteristic features met with in this malady, viz., much diminished gastric motility, the opaque substance not entering the duodenum until between three-quarters and one hour after ingestion and not having entirely left the stomach within seven hours. It may be stated that the child returned to hospital for a second barium meal five weeks after dismissal, i.e., at the age of thirteen weeks, and that exactly the same result was obtained.

The behaviour of the chloride metabolism in this case seems to be of particular interest and importance. On admission to hospital the urinary chlorides were normal in amount (·24 gm. per cent.) and they continued at this level during the first week of residence, registering ·24 gm. per cent. on the eighth day, but on the eleventh day, i.e., the day following the onset of food regurgitation, they had fallen to ·06 gm. per cent., and on the fifteenth day, i.e., the day following the two explosive vomits, chlorides were absent from the urine. On the succeeding day chloride excretion began again but continued low throughout the remainder of the residence in spite of the fact that no more vomiting occurred, the child was receiving an ample diet, and was steadily increasing in weight.

A fall in, or even the complete absence of, urinary chlorides is one of the most characteristic features of hypertrophic pyloric stenosis. Although generally attributed to the vomiting, it has never been possible to correlate the degree of the fall with the severity of the vomiting. This fall in chlorides is, on the other hand, one of the rarest occurrences in vomiting, and even severe and prolonged vomiting, from any other cause than pyloric stenosis. These facts have always cast doubt on the view that the whole explanation is to be found in the loss of HCl in the gastric juice. While it is admitted that there was some vomiting in this case, and hence a possible cause of chlorine depletion, it is difficult to believe that the deprivation resulting from only two explosive vomits during the course of forty-eight hours, was sufficient to account for the complete absence of chlorine from the urine.

I have seen one other case of hypertrophic pyloric stenosis (confirmed at autopsy) in which there was no history of vomiting and in which vomiting never once occurred during a residence of four weeks in hospital. Nevertheless, this particular child developed a most severe degree of alkalosis (indeed it was the presence of this state that led to a careful examination of the abdomen and the detection of a pyloric tumour and visible gastric peristalsis) as shown by slow shallow breathing and a blood CO_2 content of 102 vol. per cent. so that in all probability there was also a fall in the

blood and urinary chlorides though unfortunately neither of these estimations was carried out.

The findings in these two undoubted examples of hypertrophic pyloric stenosis surely suggest that it is some factor other than vomiting which is responsible for the fall in the urinary chlorides.

It will be recalled that Haden and Orr[1] in the first instance suggested as an explanation for the absence of chloride excretion in pyloric stenosis that the chlorine was fixed in the tissues by some toxin, and that later Drake and Tisdall[2] showed that the injection of histamin led to a low blood chloride content which could not be attributed to vomiting. At first the low chloride content of the tissues in pyloric stenosis demonstrated by Morris and Graham[3], and the high retention of chlorine when administered intravenously[4], seemed to negative this explanation, but the finding of Morris and Morris[5] that the chlorine is present in organic and inorganic combination, and that the former exists in a volatile and a non-volatile form, suggested that the original hypothesis of Haden and Orr might be after all correct.

It may be that not only is the chlorine deflected to the tissues but that in addition a greater proportion is present in the volatile form and therefore not readily estimated. Was it the development of pyloric spasm in the present case, as indicated by the regurgitation, that precipitated the change in chlorine metabolism? In support of such a hypothesis the usually more rapid rise in the urinary chlorides to the normal level after the cessation of vomiting in those cases submitted to operation than in those treated medically may be instanced. It is assumed that by means of the operation all spasm must be immediately relieved.

In conclusion, attention is drawn to the variation of the symptomatology in different examples of hypertrophic pyloric stenosis, and it is suggested that it is this factor which accounts for the varying experience of different workers regarding the efficacy of eumydrin. These physicians who have had under their care a larger proportion of mild cases will have good results to record, whereas those who have had a high proportion of severe cases will have had the reverse experience. In the present case it is felt that any variety of medical treatment would have succeeded, so mild, if not indeed non-existent, were the symptoms. However, such a successful issue has not been a usual experience. Ever since Svensgaard[6] reported her success with this line of treatment eumydrin has been given a trial in all examples of this condition coming under observation, but as yet it is only in the minority that it has proved efficacious and spared the necessity of operative interference. Nevertheless, as eumydrin often acts in a most unexpected fashion, it should always be given a trial.

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PAPILLOMA OF THE CHOROID PLEXUS IN AN INFANT

BY

J. H. EBBS, M.D., D.C.H.

(The Children's Hospital, Birmingham.)

Friedman and Solomon[1] have recently reviewed the literature relating to papilloma of the choroid plexus and have tabulated in detail the fifteen cases which have been reported in children. The following case record of this rare condition is presented in order to illustrate a cause of hydrocephalus in young children, which is seldom considered in the differential diagnosis.

Clinical record

B. S., a fourteen-month old infant, was admitted to hospital under the care of Dr. Smallwood, eleven weeks before death with the complaint of cough since the age of three months. This became worse after measles at the age of six months. The cough was always worse in the morning and had been increasing in severity. The infant had been born at full term and was normal in development. There was no known contact with tuberculosis.

Physical and x-ray examination revealed a post-pneumonic fibrosis and bronchiectasis. The child slowly lost weight in the hospital but otherwise appeared well, apart from cough. Eight weeks before death the fontanelle was noticed to be full, and later definitely bulging. There was a slowly increasing hydrocephalus. Vomiting became frequent. Lumbar puncture revealed a blood-stained cerebro-spinal fluid. The left arm and leg moved more than the right. The right plantar response was extensor, the left was flexor. Finally both became extensor. The general condition continued to get worse until the child died suddenly, eleven weeks after admission to the hospital.

Examinations of the cerebro-spinal fluid were made frequently. The leucocytes were never increased. The red blood cells varied from 0 to 850 per c.mm., but usually were less than 100. Bio-chemical analysis of the cerebro-spinal fluid revealed normal values for sugar, and protein, with a slightly reduced chloride content, varying from 683 to 635 mgm. per cent. Tubercle bacilli were searched for by direct examination and guinea-pig inoculation, but none were found. The Wassermann reaction was negative. The red blood cells and leucocytes were normal in number and type. A clinical diagnosis of idiopathic hydrocephalus was made.

Post-mortem findings

At post-mortem examination the brain was soft and showed marked internal hydrocephalus, which was equal on the two sides. The choroid plexus in the left lateral ventricle was normal. That on the right side presented a

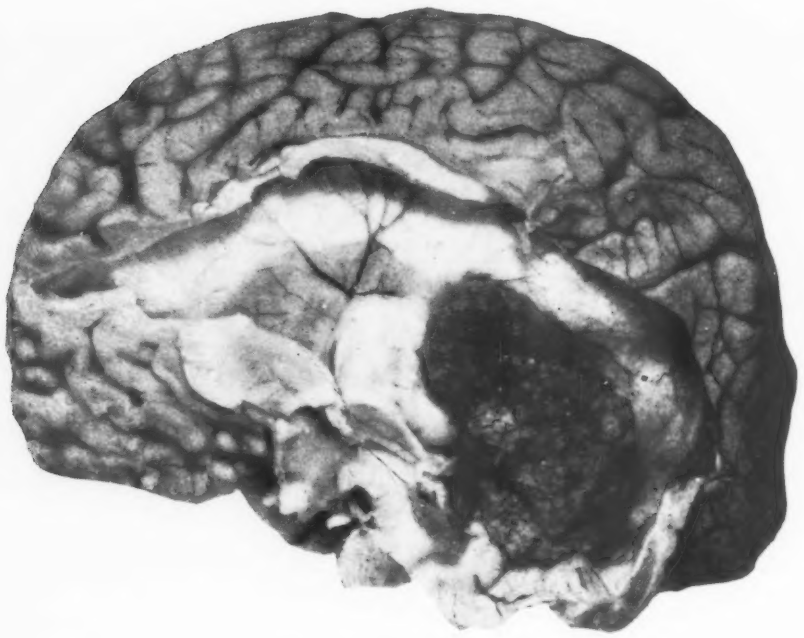

FIG. 1.—Right ventricle.

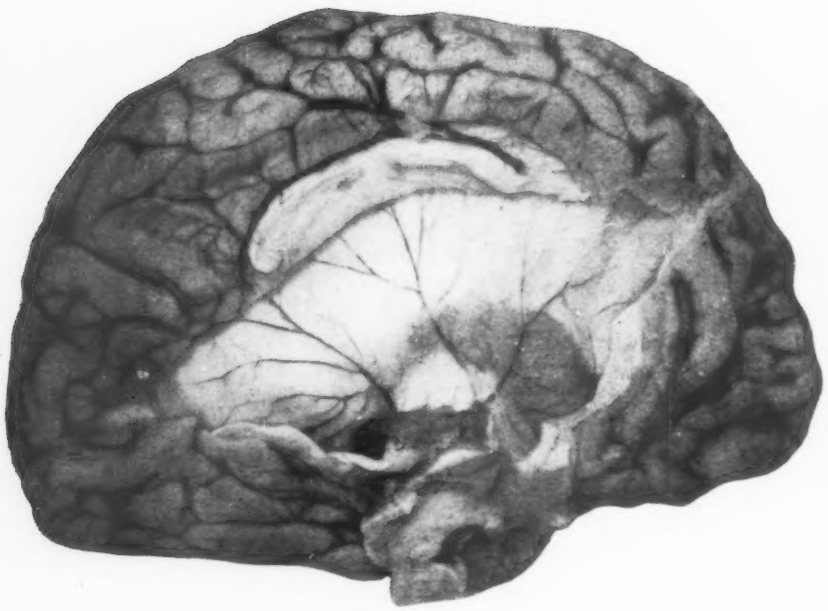

FIG. 2.—Left ventricle.

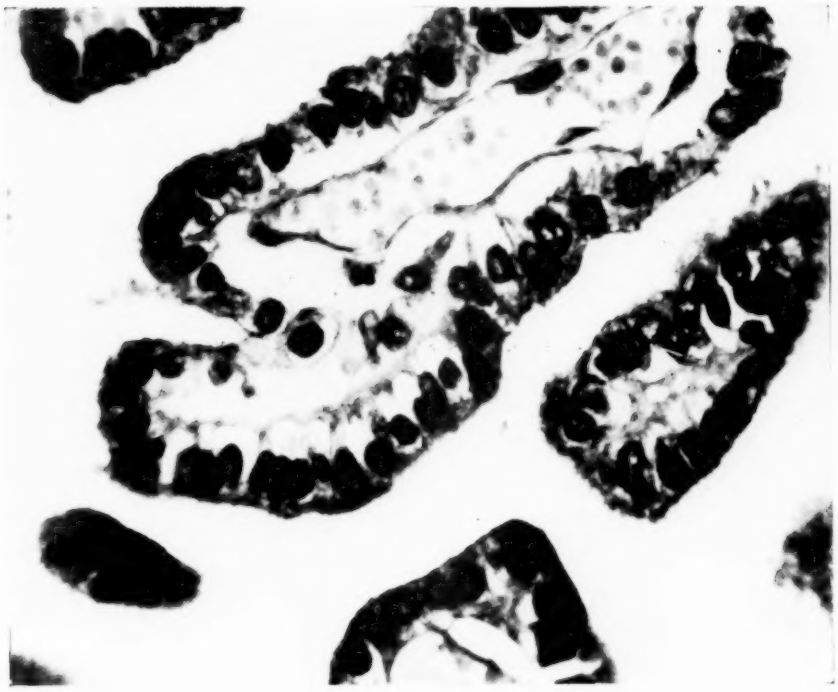

FIG. 3.

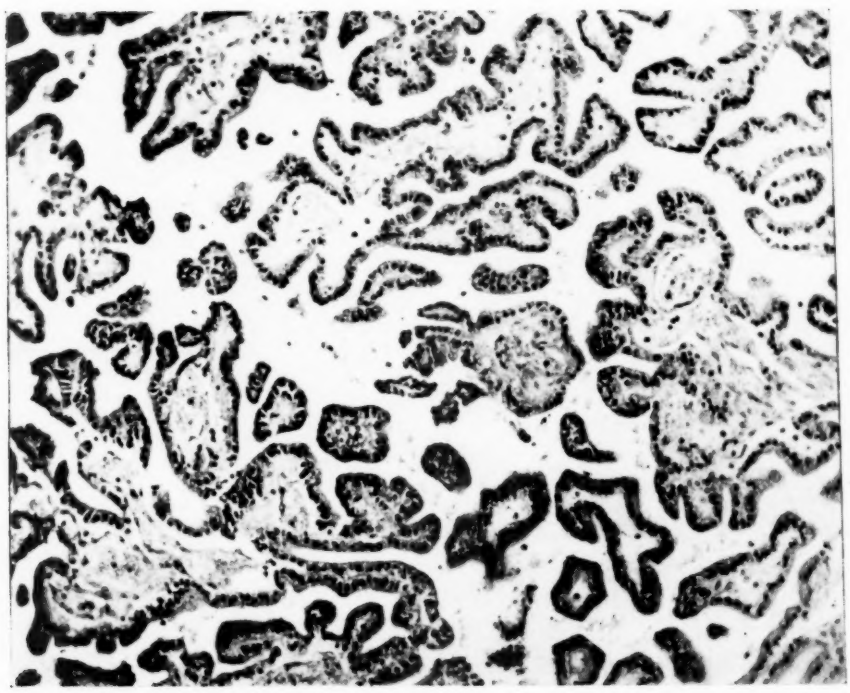

FIG. 4.

large, soft, sponge-like mass about the size of a hen's egg, which projected from the posterior horn of the ventricle (see fig. 1 and 2). When floated in water the tumour was extremely soft, velvety and easily compressible. There was no surface lining. Palpation revealed no cystic spaces or calcareous deposits.

Microscopically the mass was composed of long papillae with numerous branches and projecting villi (see fig. 3 and 4). These consisted of typical connective tissue with numerous thin-walled capillaries composing a large part of their structure. The lining epithelium consisted of a single layer of cuboidal cells, which in some parts appeared almost as columnar epithelium. The cells were uniform in size and the round or oval nuclei stained deeply. Numerous vacuoles were present, usually one large vacuole at the fixed end of the cell. The picture was the same in all areas being one of a simple hypertrophy of the choroid plexus, showing no evidence of malignancy, invasion or necrosis.

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EDITED BY

CHARLES HARRIS, M.D., F.R.C.P., and ALAN MONCRIEFF, M.D., F.R.C.P.

WITH THE HELP OF

H. C. CAMERON, M.D., F.R.C.P.
H. A. T. FAIRBANK, D.S.O., M.S., F.R.C.S.
LEONARD FINDLAY, D.SC., M.D., F.R.C.P.
A. DINGWALL FORDYCE, M.D., F.R.C.P.ED.
REGINALD MILLER, M.D., F.R.C.P.
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LEONARD G. PARSONS, M.D., F.R.C.P.
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